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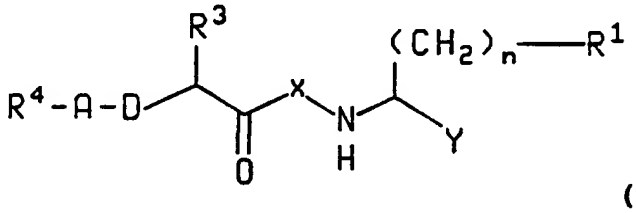

(I)

(57) Abstract

A compound of formula (I) which is effective for treating or preventing hypertension, congestive heart failure, myocardial infarction, cardiac and left ventricular hypertrophy, coronary artery disease including myocardial infarction, vascular hypertrophy, and vascular damage following diabetic and non-diabetic renal disease, and vascular damage associated with angioplasty and aetheroma.

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INHIBITORS OF ANGIOTENSIN I CHYMASE(S) INCLUDING HUMAN HEART CHYMASE

Background of the Invention

This invention relates to novel polypeptides. These compounds are useful for treatment of hypertension, congestive heart failure, cardiac hypertrophy including left ventricular hypertrophy, peripheral vascular complications, diabetic complications including renal disease, and other degenerative disorders mediated by angiotensin II.

Certain chymases, a subfamily of serine proteases, including human heart chymase, human mast cell chymase, and human skin chymase (which if not all the same, are very closely related enzymes), have been found to cleave the naturally occurring decapeptide known as angiotensin I to the octapeptide known as angiotensin II, without substantially degrading angiotensin II. These enzymes are termed herein angiotensin I chymases.

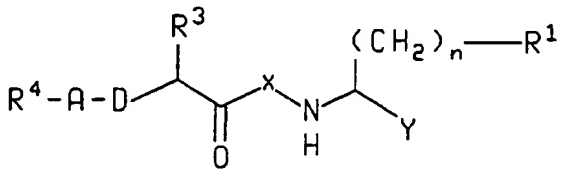
Angiotensin II is known to be a potent pressor substance, i.e. a substance that is capable of inducing a significant increase in blood pressure and is believed to act by causing the constriction of blood vessels and the release of the sodium-retaining hormone aldosterone from the adrenal gland. Angiotensin II is also produced from the decapeptide angiotensin I by the action of angiotensin converting enzyme (ACE). The ACE pathway is the target of a number of therapeutically useful antihypertensive agents.

Therefore, angiotensin I chymases, including human heart chymase, provide an ACE-independent pathway for formation of angiotensin II, and are thus implicated as a causative factor in certain forms of hypertension and congestive heart failure. Angiotensin II is also implicated as a causative agent in other diseases or risk factors associated with hypertension, such as cardiac hypertrophy (enlargement of the heart), myocardial infarction, vascular hypertrophy (proliferation of vascular smooth muscle cells), diabetic and nondiabetic renal disease (caused in part by hypertension in the kidney), and restenosis or vascular damage in blood vessels of patients suffering from aetheroma treated with angioplasty techniques or thrombolytics. It is a current goal of antihypertensive therapy to treat or prevent such damage to organs or vessels in addition to lowering blood pressure. Angiotensin I chymases, including human heart chymase, are thereby implicated as causative factors in the above-named degenerative disorders in addition to hypert nsion and cong stiv heart failur .

One means of alleviating or preventing the above mentioned adverse effects and diseases produced by angiotensin II is the administration of a substance capable of inhibiting the angiotensin I cleaving action of chymase, including human heart chymase.

Summary of the Invention

The present invention relates to compounds of the formula



I

wherein n is one or two;

R^1 is phenyl, naphthyl, $(C_3\text{-}C_7)$cycloalkyl, unsaturated heterocycle, or benzo-fused unsaturated heterocycle; wherein said unsaturated heterocycle is selected from pyrrolyl, pyrrolinyl, furyl, dihydrofuryl, thienyl, dihydrothienyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolinyl, imidazolyl, imidazolinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzofused-unsaturated heterocycle is selected from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl and benzoxazinyl; wherein each of said phenyl, naphthyl, unsaturated heterocycle and benzofused unsaturated heterocycle may optionally be substituted with from one to three substituents, said substituents being independently selected from bromo, chloro, fluoro, $(C_1\text{-}C_5)$alkyl, $(C_1\text{-}C_5)$alkoxy, $(C_1\text{-}C_5)$alkylthio, $(C_1\text{-}C_5)$alkylamino, $(C_1\text{-}C_4)$alkylsulfonyl, $(C_1\text{-}C_5)$dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl, $-\overset{O}{\overset{\|}{C}}O(C_1\text{-}C_5)$alkyl, $-\overset{O}{\overset{\|}{C}}NH_2$, $-\overset{O}{\overset{\|}{C}}NH(C_1\text{-}C_5)$alkyl, $-\overset{O}{\overset{\|}{C}}N\text{-di}(C_1\text{-}C_5)$alkyl, and formyl; and wherein said $(C_3\text{-}C_7)$cycloalkyl may optionally be substituted with from one to three substituents,

said substituents being independently selected from bromo, chloro, fluoro, (C_1-C_6)alkyl, (C_1-C_5)alkylthio, (C_1-C_5)alkoxy, hydroxy, trifluoromethyl and oxo (O=);

R^3 is (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_2)alkyl, (C_1-C_5)alkylthio(C_1-C_2)alkyl, phenyl, unsaturated heterocycle, phenyl(C_1-C_2)alkyl, or unsaturated heterocycle(C_1-C_2)alkyl; wherein said unsaturated heterocycle is as defined for R^1; wherein said unsaturated heterocycle(C_1-C_2)alkyl is an unsaturated heterocycle moiety as defined in R^1, wherein any one of the carbon atoms of said unsaturated heterocycle moiety is substituted with (C_1-C_2)alkyl; wherein said (C_1-C_5)alkyl, (C_3-C_6)cycloalkyl(C_1-C_5)alkyl and (C_3-C_6)cycloalkyl may optionally be substituted with one or more fluorine atoms; wherein each of said phenyl, unsaturated heterocycle, phenyl(C_1-C_2)alkyl, and unsaturated heterocycle(C_1-C_2)alkyl may optionally be substituted on the ring atoms with from one to three substituents, said substituents being independently selected from the functionalities set forth in the definition of R^1 for the substituents on said phenyl;

R^4 is selected from the functionalities listed in groups (a) - (d) below:

a) piperazino, piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl and azetidino, wherein any of the carbon atoms of said piperazino may optionally be substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, (C_1-C_5)alkylthio(C_1-C_3)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, and (C_1-C_5)dialkylamino(C_1-C_3)alkyl; wherein the nitrogen in the 4 position of said piperazino may optionally be substituted with (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_2-C_4)alkyl, hydroxy(C_2-C_4)alkyl, amino(C_2-C_4)alkyl, (C_1-C_5)alkylamino(C_2-C_4)alkyl, (C_1-C_5)dialkylamino(C_2-C_4)alkyl, and 2,2,2-trifluoroethyl; wherein any of the carbon atoms of said piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl and azetidino may optionally be substituted with one or two substituents, said substituents being independently selected from chloro, bromo, fluoro, hydroxy, (C_1-C_5)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, (C_1-C_5)alkoxy(C_1-C_3)alkyl, (C_1-C_5)alkoxy, (C_1-C_5)alkoxy(C_1-C_3)alkoxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, (C_1-C_5)alkylthio, oxo (O=), unsaturated heterocycle, azetidino, pyrrolidino, piperidino, morpholino, 4-oxopiperdino, 4-hydroxypip ridino and piperazino, wherein th nitrogen in the 4 position of said piperazino may optionally be substituted with (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_2-C_4)alkyl, hydroxy(C_2-C_4)alkyl, amino(C_2-C_4)alkyl, (C_1-C_5)alkylamino(C_2-C_4)alkyl, (C_1-

C_5)dialkylamino(C_2-C_4)alkyl, or 2,2,2 trifluoroethyl; wherein said unsaturated heterocycle is as defined in R^1; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle;

b) 4-morpholino, 4-thiomorpholino, 1-oxothiomorpholino, or 1,1-dioxothiomorpholino; wherein any of the carbon atoms of said 4-morpholino, 4-thiomorpholino, 1-oxothiomorpholino, and 1,1 dioxothiomorpholino may optionally be substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, (C_1-C_5)alkylthio(C_1-C_3)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl and (C_1-C_5)dialkylamino(C_1-C_3)alkyl;

c) (C_1-C_7)alkyl or (C_3-C_7)cycloalkyl; wherein said (C_3-C_7)cycloalkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from halo, hydroxy, (C_1-C_5)alkoxy, (C_1-C_5)alkoxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, (C_1-C_5)alkylthio(C_1-C_3)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl,(C_1-C_5)dialkylamino(C_1-C_3)alkyl,(C_1-C_5)alkoxy(C_1-C_3)alkyloxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, (C_1-C_5)alkylthio, azetidino, pyrrolidino, piperidino, piperazino, 4-(C_1-C_5)alkylpiperazino, morpholino, thiomorpholino, oxothiomorphilino, dioxothiomorpholino, 4-oxopiperidino, 4-hydroxypiperidino, and unsaturated heterocycle, wherein said unsaturated heterocycle is defined as in R^1; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle; wherein said (C_1-C_7)alkyl may optionally be substituted with one to three substituents, said substituents being independently selected from halo, hydroxy, (C_1-C_5)alkoxy, (C_1-C_5)alkoxy(C_1-C_3)alkyloxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, (C_1-C_5)alkylthio, azetidino, pyrrolidino, piperidino, piperazino, 4-(N)-(C_1-C_5)alkylpiperazino, morpholino, thiomorpholino, oxothiomorpholino, dioxothiomorpholino, 4-oxopiperidino, 4-hydroxypiperidino, and unsaturated heterocycle; wherein said unsaturated heterocycle is defined as in R^1; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle;

d) (R^5E)-, wherein E is oxygen, -NH or -N(C_1-C_5)alkyl, and wherein R_5 is (C_1-

C_5)alkyl, 2,2,2 trifluoroethyl, $R^7(C_2\text{-}C_4)$alkyl, $R^7C(=O)(C_2\text{-}C_4)$alkyl, $R^7C(=O)\text{-}N(C_1\text{-}C_6\text{alkyl})\text{-}(C_2\text{-}C_4)$alkyl, unsaturated heterocycle$(C_2\text{-}C_4)$alkyl, amino$(C_2\text{-}C_4)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_2\text{-}C_4)$alkyl, $(C_1\text{-}C_5)$dialkylamino$(C_2\text{-}C_4)$alkyl, $(C_1\text{-}C_5)$dialkylamino$(C_2\text{-}C_4)$alkyl, $(C_1\text{-}C_5)$alkoxy$(C_2\text{-}C_4)$alkyl or hydroxy$(C_2\text{-}C_4)$alkyl; wherein said unsaturated heterocycle$(C_2\text{-}C_4)$alkyl is an unsaturated heterocycle moiety as defined in R^1, wherein one of the ring atoms of said unsaturated heterocycle moiety of said unsaturated heterocycle$(C_2\text{-}C_4)$alkyl so defined is substituted with $(C_2\text{-}C_4)$alkyl; wherein said unsaturated heterocycle$(C_2\text{-}C_4)$alkyl may optionally be substituted on any of the ring atoms with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle;

R^7 is azetidino, pyrrolidino, piperidino, piperazino, 4-(N)-$(C_1\text{-}C_5)$alkylpiperazino, thiomorpholino, oxothiomorpholino, dioxothiomorpholino or morpholino;

A is carbonyl or sulfonyl;

D is NH, N$(C_1\text{-}C_5)$alkyl, CH_2, oxygen, CH(OH), or CH-O-$(C_1\text{-}C_5)$alkyl;

X is proline, 2-piperidinecarboxylic acid or 2-azetidinecarboxylic acid, wherein said proline, 2-piperidinecarboxylic acid and 2-azetidinecarboxylic acid may optionally be substituted with one or two substituents, said substituents being independently selected from bromine, chlorine, fluorine, $(C_1\text{-}C_5)$alkyl, $(C_1\text{-}C_3)$alkoxy, oxo, and hydroxy;

Y is BF_2, $B(OM)_2$, $-C(=O)\text{-}Z$ or $-C(OH)_2Z$, wherein M is hydrogen, or $(C_1\text{-}C_5)$alkyl, wherein the two M substituents may optionally form, together with the boron atom and the two oxygen atoms to which they are attached, a saturated heterocyclic ring containing the boron atom, 2 oxygen atoms and 2 or 3 carbon atoms, and wherein any of the carbon atoms of said heterocyclic ring may optionally be substituted with one or two $(C_1\text{-}C_5)$alkyl groups;

Z is selected from CF_2R^{11}, $CF_2C(=O)N(R^{13})R^{12}$, $C(=O)N(R^{13})R^{12}$, $C(=O)OR^{12}$ or a

heterocycle selected from 2-oxazolyl, 2-thiazolyl, 2-imidazolyl, 2-thienyl, 2-furyl, 2-pyrrolyl, 5-tetrazolyl, 2-benzothiazolyl, 2-benzoxazolyl, 2-benzimidazolyl, 2-benzofuryl, 2-benzothienyl and 2-indolyl; wherein said heterocycle may optionally be substituted with one to three substituents, said substituents being independently selected from (C_1-C_3)alkoxy, bromo,

chloro, fluoro, (C_1-C_3)alkyl, hydroxy, amino, nitro, cyano, $-CO(C_1$-$C_5)$alkyl, $-CNH_2$,

formyl, (C_1-C_5)alkylthio, (C_1-C_5)alkylamino, $-CF_3$, (C_1-C_4)alkyl-SO_2-, trifluoromethyl, and (C_1-C_5)dialkylamino;

R^{11} is hydrogen, fluorine, (C_1-C_5)alkyl, (C_1-C_6)perfluoroalkyl, amino (C_1-C_5)alkyl, (C_1-C_5)alkylamino(C_1-C_5)alkyl, di(C_1-C_5)alkylamino(C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_5)-alkyl or hydroxy(C_1-C_5)alkyl;

R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_5)alkyl, (C_3-C_5)alkenyl, and R^7(C_2-C_4)alkyl, wherein R^7 is defined as above;

with the proviso that (a) no carbon alpha to a ring nitrogen in the substituent R^4 may be directly bonded to a halogen, oxygen or nitrogen substituent, (b) when X is substituted proline, 2-piperidinecarboxylic acid or 2-azetidinecarboxylic acid, then no fluorine, oxo, (C_1-C_3)alkoxy or hydroxy substituent is present on either of the ring carbon atoms adjacent to the nitrogen atom of said proline, 2-piperidinecarboxylic acid or 2-azetidinecarboxylic acid, and (c) the compound of formula I can not be defined as a compound wherein n is one, R^1 is phenyl, R^3 is phenyl(C_1-C_2)alkyl, R^4 is (R^5E)- wherein E is oxygen and R^5 is (C_1-C_5)alkyl, A is carbonyl, D is NH, X is proline and Y is $B(OM)_2$.

Preferred compounds of formula I are those wherein:

n is 1;

R^1 is phenyl or (C_3-C_7)cycloalkyl, wherein said phenyl or (C_3-C_7)cycloalkyl may optionally be substituted as defined in R^1 of formula I above;

R^3 is (C_1-C_5)alkyl, hydroxy(C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_2)alkyl, (C_1-C_5)alkylthio(C_1-C_2)alkyl, phenylmethyl, 4-imidazolylmethyl or 4-thiazolylmethyl; wherein any of the carbon atoms of said (C_1-C_5)alkyl may optionally be substituted with one or more fluorine atoms; and wherein from one to three carbon atoms of the phenyl moiety of said phenylmethyl may optionally be substituted with any of the functionalities set forth in the definition of R^1 of formula I for the substituents on said phenyl;

R^4 is selected from the functionalities listed in groups (a)-(d) below:

a) piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl and azetidino; wherein the nitrogen in the 4-position of said piperazino may optionally be substituted with any of the functionalities set forth in the definition of R^4(a) of formula I for the substituents on the nitrogen in the 4-position of piperazino; wherein any of the ring carbon atoms of said piperazino, piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl and azetidino may optionally be substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, amino (C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, hydroxy, oxo(O=), (C_1-C_5)alkoxy(C_1-C_3)alkoxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-C_5)alkylpiperazino, morpholino, and unsaturated heterocycle; wherein said unsaturated heterocycle is as defined in R^1; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set for in the definition of R^1 of formula I for the substituents on said unsaturated heterocycle;

b) morpholino optionally substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, and (C_1-C_5)dialkylamino(C_1-C_3)alkyl;

c) (C_1-C_7)alkyl and (C_3-C_7)cycloalkyl; wherein said (C_1-C_7)alkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-C_5)alkylpiperazino and morpholino; wherein said (C_3-C_7)cycloalkyl may optionally be substituted with one to three substituents, said substituents being independently selected from amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, azetidino, pyrrolidino, pip ridino, piperazino, 4-N-(C_1-C_5)alkylpiperazino, morpholino and unsaturated heterocycl , wher in said unsaturated

heterocycle is as defined above in R^1 of formula I; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 of formula I for the substituents on said unsaturated heterocycle;

d) (R^5E)-, wherein E is oxygen or -N(C_1-C_5)alkyl, and wherein R^5 is (C_1-C_5)alkyl, 2-(pyridyl)ethyl, di(C_1-C_5)alkylaminoethyl, di(C_1-C_5)alkylaminopropyl, 2-(R^7C)ethyl or 2-[R^7CN(C_1-C_5)alkyl]ethyl;

R^7 is azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-C_5)alkylpiperazino, thiomorpholino, oxothiomorpholino, dioxothiomorpholino or morpholino;

A is carbonyl or sulfonyl;

D is NH, CH_2 or oxygen;

X is proline;

Y is -C-Z or $-C(OH)_2Z$;

Z is CF_3, CO_2R^{12}, $-C(=O)-N(R^{13})-R^{12}$, $-CF_2C(=O)N(R^{13})-R^{12}$,

or a heterocycle selected from 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl; wherein said 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl may optionally be substituted with from one to three substituents independently selected from (C_1-C_3)alkoxy, bromo, chloro, fluoro, (C_1-C_3)alkyl, hydroxy, amino, nitro, cyano, $-CO(C_1$-$C_5)$alkyl, $-CNH_2$, formyl, (C_1-C_5)alkylthio, (C_1-C_5)alkylamino, $-CF_3$, (C_1-C_4)alkyl-SO_2-, trifluoromethyl, and (C_1-C_5)dialkylamino;

R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_5)alkenyl, and R^7(C_2-C_4)alkyl, wherein R^7 is defined as abov ;

with th proviso that (a) no carbon alpha to a ring nitrogen in the substituent R^4 may b dir ctly bonded to a halogen, oxygen or nitrogen substituent, (b) when X is

substituted proline, then no fluorine, oxo, $(C_1$-$C_3)$alkoxy or hydroxy substituent is present on either of the ring carbon atoms adjacent to the nitrogen atom of said proline, and (c) when E is oxygen R^5 is $(C_1$-$C_5)$alkyl; and (d) when E is $N(C_1$-$C_5)$alkyl, R^5 is selected

from 2-(pyridyl)ethyl, di$(C_1$-$C_5)$alkylaminoethyl, di$(C_1$-$C_5)$alkylaminopropyl, 2-(R^7C(=O))ethyl and 2-[R^7CN(C_1-C_5)alkyl]ethyl.

More preferred compounds of formula I are the foregoing preferred compounds wherein R^1 is cyclohexyl or phenyl; R^3 is $(C_1$-$C_5)$alkyl, phenylmethyl, 4-imidazolylmethyl, or 4-thiazolylmethyl;

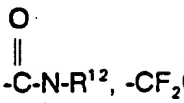
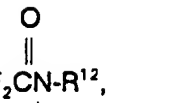
R^4 is piperazino, 4-N-$(C_1$-$C_5)$alkylpiperazino, morpholino, piperidino, 3-azabicyclo[3.1.0]hex-3-yl, 2-$(C_1$-$C_5)$dialkylamino$(C_1$-$C_3)$alkylmorpholino, or $(C_3$-$C_7)$cycloalkyl; wherein said piperidino and 3-azabicyclo[3.1.0]hex-3-yl may optionally be substituted with one or two substituents, said substituents being independently selected from $(C_1$-$C_5)$alkyl, amino$(C_1$-$C_3)$alkyl, $(C_1$-$C_5)$alkylamino$(C_1$-$C_3)$alkyl, $(C_1$-$C_5)$dialkylamino$(C_1$-$C_3)$alkyl, hydroxy, oxo, $(C_1$-$C_5)$alkoxy, $(C_1$-$C_5)$alkoxy$(C_1$-$C_3)$alkyloxy, amino, $(C_1$-$C_5)$alkylamino, $(C_1$-$C_5)$dialkylamino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, 4-N-$(C_1$-$C_5)$alkylpiperazino and unsaturated heterocycle; wherein said unsaturated heterocycle is as defined in R^1 of formula I; wherein said unsaturated heterocycle may optionally be substituted with one to three substituents independently selected from the functionalities set forth in the definition of R^1 of formula I for the substituents on said unsaturated heterocycle; wherein said $(C_3$-$C_7)$cycloalkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from hydroxy, oxo (=O), $(C_1$-$C_5)$alkoxy, amino, $(C_1$-$C_5)$alkylamino, $(C_1$-$C_5)$dialkylamino, amino$(C_1$-$C_3)$alkyl, $(C_1$-$C_5)$alkylamino$(C_1$-$C_3)$alkyl, $(C_1$-$C_5)$dialkylamino$(C_1$-$C_3)$alkyl, azetidino, pyrrolidino, piperidino, piperazino, 4-N-$(C_1$-$C_5)$piperazino, morpholino, and unsaturated heterocycle; wherein said unsaturated heterocycle is as defined in R^1 of formula I; wherein said unsaturated heterocycle may optionally be substituted with one to three substituents independently selected from the functionalities set forth in th definition of R^1 of formula I for the substituents on said unsaturat d het rocycle;

A is carbonyl or sulfonyl;

D is NH, CH_2 or oxygen;

X is proline;

Y is  or $-C(OH)_2Z$;

Z is CF_3, CO_2R^{12},  ,  ,

or a heterocycle selected from 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl; wherein said 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl may optionally be substituted with from one to three substituents independently selected from $(C_1\text{-}C_3)$alkoxy, bromo, chloro, fluoro, $(C_1\text{-}C_3)$alkyl, hydroxy, amino, nitro, cyano,  , formyl, $(C_1\text{-}C_5)$alkylthio, $(C_1\text{-}C_5)$alkylamino, $-CF_3$, $(C_1\text{-}C_4)$alkyl-SO_2-, trifluoromethyl, and $(C_1\text{-}C_5)$dialkylamino;

R^{12} and R^{13} are independently selected from hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$alkenyl, and $R^7(C_2\text{-}C_4)$alkyl, wherein R^7 is defined as above;

with the proviso that (a) no carbon alpha to a ring nitrogen in the substituent R^4 may be directly bonded to a halogen, oxygen or nitrogen substituent,and (b) when X is substituted proline, then no fluorine, oxo, $(C_1\text{-}C_3)$alkoxy or hydroxy substituent is present on either of the ring carbon atoms adjacent to the nitrogen atom of said proline.

Specific preferred compounds of Formula I are:

N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide;

N-[(1,1-dimethyethoxy)carbonyl]-L-valyl-N-[2,3-dioxo-3-methoxy-1-(ph nylmethyl)propyl]-L-prolinamide;

N-[4-[N-methylamino]pip ridine-1-carbonyl]-L-valyl-N-[3,3,3-trifluor -2-oxo-1(S)-(ph nylmethyl)propyl]-L-prolinamide hydrochloride;

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride;

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[2,3-dioxo-3-1-methylethoxy-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride;

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[2,3-dioxo-3-1-methylethoxy)-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride;

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-((1-methyl)ethoxy)-1-(phenylmethyl)propyl]-L-prolinamide; and

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-((1-methyl) ethoxy)-1(S)-(phenylmethyl)propyl]-L-prolinamide.

The present invention also includes compounds of formula I wherein

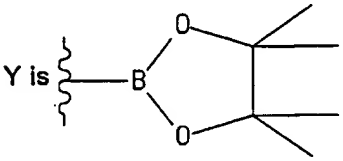
a) R^4 is [1α, 5α, 6α]-6-(dimethylamino)-3-azabicyclo[3.1.0]hex-3-yl, A is carbonyl, D is NH, R^3 is isopropyl, X is proline, Y is C(=O)Z wherein Z is CF_3, n is 1 and R^1 is phenyl;

b) R^4 is 4-methylpiperazin-1-yl, A is carbonyl, D is NH, R^3 is isopropyl, X is proline, Y is C(=O)Z wherein Z is CF_3, n is 1 and R^1 is phenyl;

c) R^4 is 4-methyl-1-piperazinyl, A is sulfonyl, D is CH_2, R^3 is isopropyl, X is proline, Y is C(=O)Z wherein Z is CF_3, n is 1 and R^1 is phenyl;

d) R^4 is 4-(dimethylamino)piperidin-1-yl, A is CO, D is NH, R^3 is isopropyl, X is proline, Y is C(=O)Z wherein Z is CF_3, n is 1 and R^1 is phenyl;

e) R^4 is 4-(methylamino)piperidin-1-yl, A is carbonyl, D is NH, R^3 is 2-butyl, X is proline, Y is C(=O)Z wherein Z is CF_3, n is 1 and R^1 is phenyl;

f) R^4 is 4-(methylamino)piperidin-1-yl, A is carbonyl, D is NH, X is proline, Y is  , n is 1, R^3 is isopropyl and R^1 is phenyl; or

g) R^4 is 4-(methylamino)piperidin-1-yl, A is carbonyl, D is NH, R^3 is isopropyl, X is proline, Y is $-BF_2$, n is 1 and R^1 is phenyl;

The present invention also includes a method of treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease (including myocardial infarction, vascular hypertrophy, and vascular damage

such as restenosis following angioplasty or aetheroma), diabetic renal disease, and non-diabetic renal disease comprising administering to a mammal, preferably a human, in need of such treatment a chymase inhibiting effective amount of a chymase inhibiting compound , or pharmaceutically acceptable salt thereof.

The present invention also includes a pharmaceutical composition for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease (including myocardial infarction, vascular hypertrophy, and vascular damage such as restenosis following angioplasty or aetheroma), diabetic renal disease, and non-diabetic renal disease comprising a chymase inhibiting effective amount of a chymase inhibiting compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also includes a method for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease (including myocardial infarction, vascular hypertrophy, and vascular damage such as restenosis following angioplasty or aetheroma), diabetic renal disease, and non-diabetic renal disease which comprises administering to a mammal, preferably a human, in need of such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disease.

The present invention also includes a pharmaceutical composition for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease (including myocardial infarction, vascular hypertrophy, and vascular damage such as restenosis following angioplasty or aetheroma), diabetic renal disease, and non-diabetic renal disease comprising an amount of a compound of the formula I that is effective in treating or preventing such disease, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also includes a method for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease (including myocardial infarction, vascular hypertrophy, and vascular damage such as r st nosis following angioplasty or aetheroma), diabetic renal disease, and non-diabetic r nal disease which comprises administering to a mammal, preferably

a human, in need of such treatment a chymase inhibiting amount of a compound of the formula I or a pharmaceutically acceptable salt thereof.

The present invention also includes a pharmaceutical composition for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease (including myocardial infarction, vascular hypertrophy, and vascular damage such as restenosis following angioplasty or aetheroma), diabetic renal disease, and non-diabetic renal disease comprising a chymase inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Preferred compositions comprise the foregoing preferred compounds.

The pharmaceutically acceptable salts of the present invention are those which are non-toxic at the dosages administered. Since compounds of the invention may contain acidic or basic groups, acid or base addition salts are possible. Pharmaceutically acceptable acid addition salts include, for example, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, maleate, mesylate, fumarate, citrate, acid citrate, tartrate, bitartrate, succinate, gluconate and saccharate salts. Pharmaceutically acceptable base addition salts are for example sodium, potassium, calcium and magnesium salts.

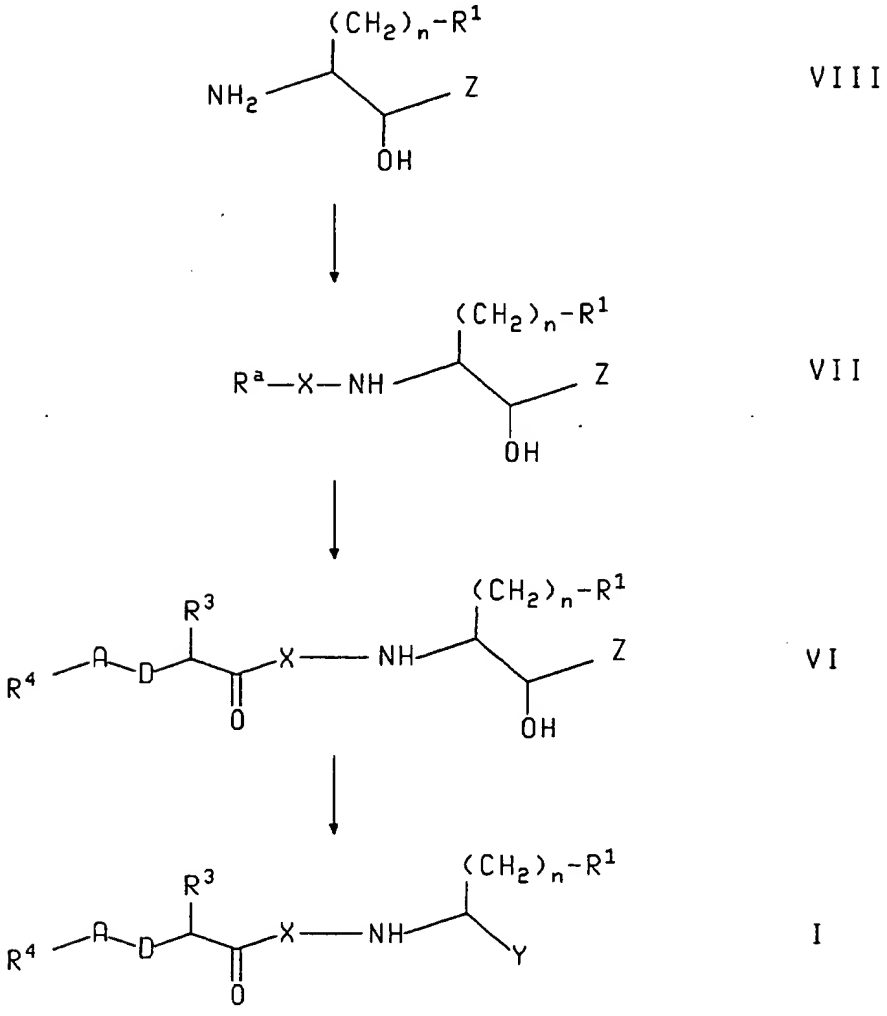
All the natural amino acids contained in the structures of the compounds of the present invention are of the L configuration, the naturally occurring configuration, unless otherwise noted.

Unless otherwise indicated, the term "alkyl", as used herein, may be straight or branched. The terms "di(C_1-C_5)alkylamino or di(C_1-C_7)alkylamino", as used herein, refer to two alkyl groups independently selected from (C_1-C_5)alkyl or (C_1-C_7)alkyl.

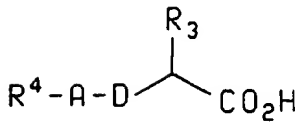
Detailed Description of the Invention

The compounds of the formula I may be prepared as described in the following reaction schemes and discussion. Unless otherwise indicated R^1, R^3, R^4, A, D, X, Y, Z and n in the reaction schemes and discussion that follow are defined as above.

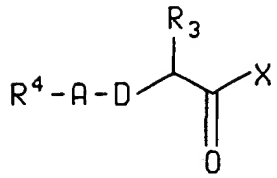
Scheme 1



Scheme 2



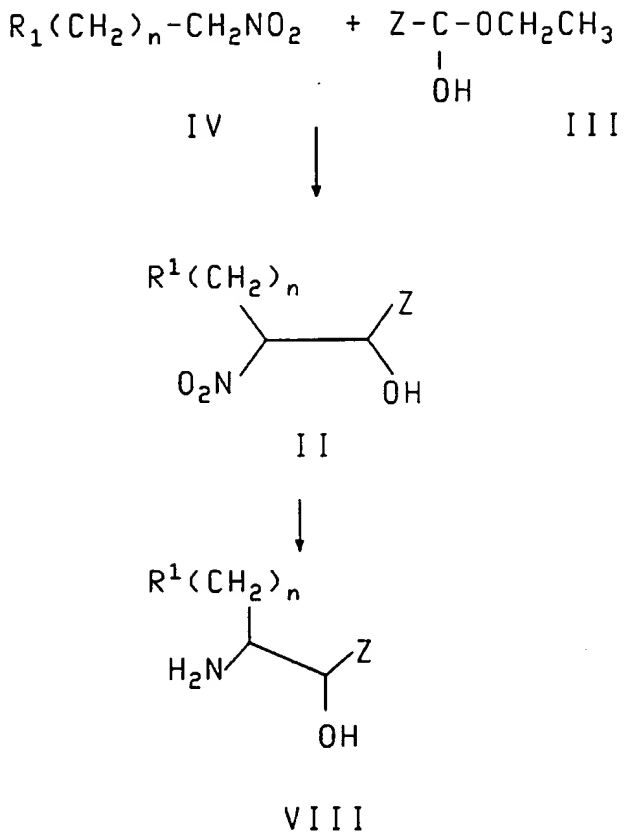
XI



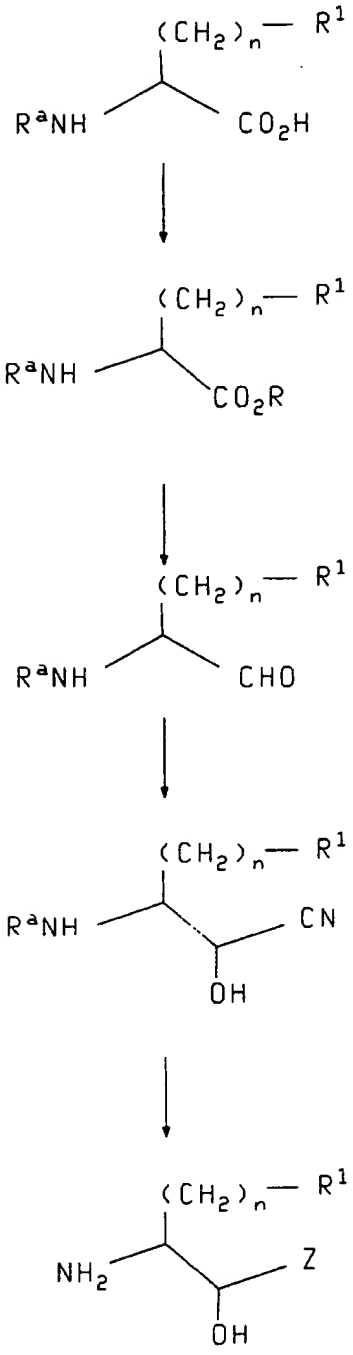
V

VI

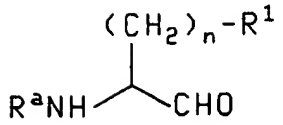
Scheme 3


R1(CH2)n-CH2NO2
+
Z-C-OCH2CH3
OH
IV
III
R1(CH2)n
Z
O2N
OH
II
R1(CH2)n
H2N
Z
OH
VIII

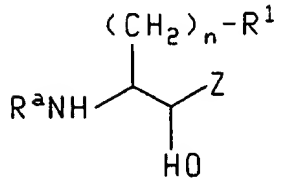
Scheme 4


(CH2)n— R1
RaNH
CO2H
X
(CH2)n— R1
RaNH
CO2R
Xa
(CH2)n— R1
RaNH
CHO
XII
(CH2)n— R1
RaNH
CN
OH
XIII
(CH2)n— R1
NH2
Z
OH
VIII

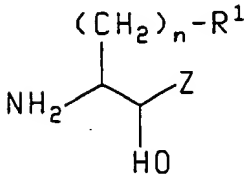
Scheme 5



XII

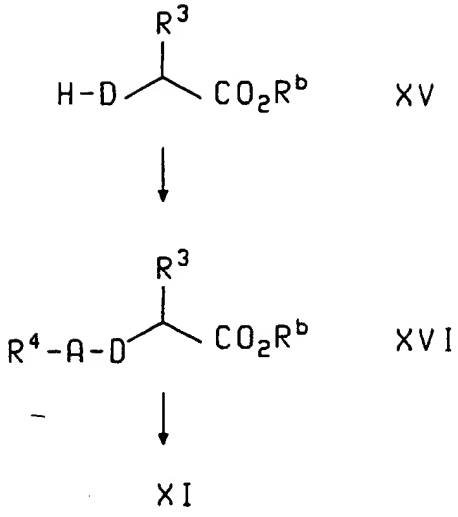


XIV

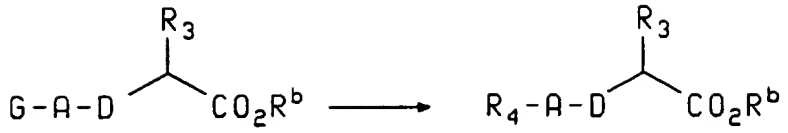


VIII

Scheme 6



Scheme 7



XVII XVI

Scheme I refers to the synthesis of compounds of formula I wherein Y is -C-Z. These compounds are prepared from compounds of formula VIII. The basic sub-unit of the preferred chemical synthesis is the coupling or acylation of the unprotected amino group of the amine residue of a compound of formula VIII with an amino acid (e.g., proline) having an activated (for acylation purposes) carboxylic function and a suitable protecting group bonded to its own alpha-nitrogen to form a peptide bond between the two amino acid residues, followed by the removal of said protecting group.

Such a coupling reaction is generally conducted at a temperature of about -30 to about 80°C, preferably about 0 to about 25°C. Examples of suitable coupling reagents which activate the carboxylic functionality of the amino acid are dicyclohexylcarbodiimide/hydroxybenzotriazole (HBT), N-3-dimethylaminopropyl-N'-ethylcarbodiimide/HBT, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), carbonyl diimidazole (CDI)/HBT, and diethylphosphorylcyanide.

The coupling is conducted in an inert solvent, preferably an aprotic solvent. Suitable solvents include acetonitrile, dichloromethane, chloroform, and dimethylformamide. The preferred solvent is dichloromethane.

For a discussion of other conditions used for coupling peptides see Houben-Weyl, Vol. XV, part II, E. Wunsch, Ed., George Theime Verlag, 1974, Stuttgart, and those described in M. Bodanszky. Principles of Peptide Synthesis, Springer-Verlag, Berlin (1984) and The Peptides. Analysis, Synthesis and Biology (ed. E. Gross and J. Meienhofer), Vols 1-5. (Academic Press, New York) 1979-1983.

The coupling product of formula VII, wherein R^a is any of the suitable protecting groups commonly used for amino group protection in peptide synthesis (Examples of such groups are carbobenzyloxy and t-butoxycarbonyl groups), is deprotected using conventional methods to provide a compound of formula VII wherein R^a is hydrogen. For example:

(a) If the protecting group, of the compound of the formula VII is carbobenzyloxy, the latter may be removed by hydrogenation with a noble metal catalyst such as palladium or palladium hydroxide on carbon in the presence of hydrogen. The hydrogenation is generally conducted at a temperature of about 0 to about 100°C, preferably about 20 to about 50°C.

(b) If the protecting group, R^a, is t-butoxycarbonyl group, such group may be removed by acidolysis. Acidolysis may be conducted with HCl in dioxane or with neat trifluoracetic acid at a temperature of about -30 to about 70°C, preferably about -5 to about 35°C.

(c) If the protecting group, R^e, is 9-fluorenylmethylenoxycarbonyl, such group may be removed by treatment with an amine base, preferably piperidine. This reaction may be run in piperidine as solvent at 10°C to about 100°C, preferably at 25°C.

The compounds of formula VII (R^a is hydrogen) are converted to compounds of formula VI by coupling, as described above, with an intermediate of the formula R^4-A-D-$CH(R^3)CO_2H$ (formula XI).

The compounds of formula VI are oxidized to compounds of formula I by methods commonly known to those skilled in the art. Examples of oxidation reactions are the Swern oxidation and variants thereof, chromium based oxidations (preferably pyridinium dichromate), Pfitzner-Moffatt and modified variants thereof, and the Dess-Martin periodinane oxidation. A preferred method, to form the compounds of formula I, wherein Y is not $COCF_3$, uses a Swern oxidation involving treatment of the alcohol of formula VI with oxalyl chloride, dimethyl sulfoxide and triethylamine in methylene chloride. In some cases, up to 10-20 equivalents of oxidizing agent is preferred.

For all Z and especially when Z is $-CF_3$, the more preferred oxidant is the Dess-Martin periodane. Four equivalents of 1,1,1,-triacetoxy-2,1-benzoxiodol-3(3H)one is added to a dry solution of the peptide in a non polar solvent such as dichloromethane and the mixture is stirred for a period of one to twenty-four hours. This procedure is described below as General Procedure C.

It will be understood that certain compounds of formula I contain tertiary amine functionality in the R_4, R_3, or R_1 moieties which, if present in a compound of formula VI could interfere with or be chemically reactive in the above-cited oxidation step which forms a compound of formula I. In such cases the Swern oxidation or modifications thereof, or Pfitzner-Moffatt oxidation, or modifications thereof are the preferred methods of oxidation, except for compounds wherein Z is CF_3.

It will also be understood that some compounds of formula I contain primary or s condary amine functional groups in the R_4, R_3 and R_1 moieties, and that during the synth sis f such compounds of formula I that this functionality is protected where it is pr sent, in th R_4, R_3 or R_1 moieties of the intermediates of the formula II, IV, V, VI,

VIII, XI, XV or XVI. Suitable protecting groups for this purpose are those suitable protecting groups commonly used for amino group protection in peptide synthesis (such as N-tert-butoxycarbonyl, N-carbo-benzyloxy, and 9-fluorenylmethylenoxy-carbonyl) which are also not chemically reactive under the coupling, protection and deprotection, or oxidation conditions described or referred to for the synthesis of compounds herein (for example, the oxidative conditions employed to convert the thus-protected intermediate of formula VI to the thus protected intermediate of formula I). The thus-protected intermediate of formula I is deprotected to the compound of formula I wherein the protecting group has been replaced by hydrogen. Methods are commonly known to those skilled in the art and are described as above. Examples 19 and 20 contained below illustrate the synthesis of such a secondary amine-containing compound of formula I wherein the intermediates of formula V and VI are employed having a methylamino functionality protected with the N-tert-butoxycarbonyl protecting group which is removed by treatment with HCl-dioxane to give a compound of formula I.

All compounds of formula I containing a tertiary amino functionality, in R_4, R_3, or R_1 including such compounds wherein Y is COF_3, can also be prepared by reductive amination of a compound of formula I having secondary amine functionality at the corresponding position of R_4, R_3, or R_1, with an appropriate carbonyl compound. A suitable procedure for this reductive alkylation is the addition of the appropriate carbonyl compound (1 to 100 equivalents) to a mixture of the compound of formula I having a secondary amine functionality, sodium cyanoborohydride (1.4-2 equivalents), and powdered 3 angstrom (Å) molecular seives in absolute methanol at 0-50°C, preferably at 20-25°C. It will be clear to one skilled in the art that amino, alkylamino, and dialkylamino substituted compounds of the formulae VI, V and C-terminally protected compounds of formulae V, XVI and XI including the properly protected variants thereof as described herein may be synthesized from the corresponding oxo-substituted compounds, by reductive amination of the latter with a salt of ammonia (e.g., NH_4Cl), an alkylamine, or a dialkylamine according to methods familiar to those skilled in the art, such as is illustrated for the conversion of an oxo-substituted compound of formula V to the corresponding methylamino-substituted compound of formula V by r ductive amination with methylamine in Exampl 19a, and conversion of the latter to a suitably prot cted R^4 amine-containing compound of formula V in

Example 19b. Thus, this reductive amination/protection method can be used not only for the synthesis of C-terminally protected compounds of formula V, but also for the synthesis of amine-containing compounds of formula VI, C-terminally unprotected compounds of formulae V, XI, and XVI and the properly N-protected variants thereof wherein the primary or secondary amine functionality is protected with one of the groups commonly employed for amine protection. Conditions for the introduction and removal of such groups are summarized by Greene in "Protecting Groups in Organic Synthesis", Wiley, NY, 1981.

Alternatively, compounds of formula VI may be synthesized as shown in Scheme 2, wherein a compound of formula XI is first coupled by standard peptide coupling methods referred to above to a C-terminally protected α-amino acid X such as, for example, proline benzyl ester to give a C-terminally protected compound of formula V.

Suitable protecting groups are those commonly used for carboxyl group protection in peptide synthesis. Examples of such groups are benzyl ester and t-butyl ester groups. The C-terminally protected compound of the formula V is deprotected using conventional methods to provide the C-terminally unprotected compound of formula V. For example:

(a) If the carboxyl group of the compound of the formula V is protected as a benzyl ester, the latter may be removed by hydrogenation with a noble metal catalyst such as palladium on carbon in the presence of hydrogen. The hydrogenation is generally conducted at a temperature of about 0 to about 100°C, preferably about 20 to about 50°C.

(b) If the carboxyl is protected as a t-butyl ester such group may be deprotected by acidolysis. Acidolysis may be conducted with HCl in dioxane or with neat trifluoracetic acid at a temperature of about -30 to about 70°C, preferably about -5 to about 35°C.

(c) If the carboxyl protecting group is an alkyl ester, the group may be removed by basic hydrolysis. Basic hydrolysis may be conducted with a suitable base (e.g., sodium hydroxide) at a temperature of about -30 to about 120°C, preferably about 0 to 80°C. The solvents used for removal of the protecting group should be inert solvents.

Suitable and preferred solvents are as described for the deprotection in Scheme 1. Th C-terminally unprotected compounds of the formula V so formed are then

coupled with a compound of the formula VIII, from Scheme I by conventional peptide coupling reactions as described above (e.g., Procedure A described below) to yield compounds of the formula VI.

Scheme 3 refers to the synthesis of compounds of formula VIII wherein Z is CF_3. Compounds of formula VIII can be prepared from compounds of formula II.

Compounds of formula II are prepared by Henry condensation (McBee, E.T., et al. J. Amer. Chem. Soc. 78:4053 (1956) of an appropriate nitroalkane of formula $R^1(CH_2)_nCH_2NO_2$ (prepared by standard methods if not otherwise available) with trifluoroacetaldehyde ethyl hemiacetal of the formula $CF_3CH(OH)OCH_2CH_3$ to provide a nitroalcohol of formula II which is obtained as a mixture of two racemic diastereomers [(2(RS), 3(RS) and [2(RS), 3(SR)]) (For example, see Example No. 18b). Caution! Similar compounds are reported to explode if distilled (EP 5,055,450). Reduction of the nitro group in a compound of formula II with an appropriate reducing agent affords a compound of formula VIII as a mixture of two racemic diastereomers ([2(RS),3(RS)] and [2(RS),3(SR)]). (For example, see Example 18c). This amine or its salt is used directly for further synthesis.

Alternatively, compounds of formula VIII wherein Z is CF_3 can also be prepared by the method of Kolb et. al. (Liebings Ann. Chem. 1990, 1-6) as adapted by Peet et. al. (J. Med. Chem. 1990, 33, 394-407) which involves a) dehydration of an N-aroyl (e.g. N-benzoyl) amino acid derivative (Aryl)-CONH-$\underset{\displaystyle (CH_2)_n\text{-}R^1}{\underset{|}{CH}}$-$CO_2H$ with acetic anhydride, to form an intermediate oxazolone, b) trifluoroacetylation of the resulting oxazolone with trifluoroacetic anhydride, c) dicarboxylation of this trifluoroacetyloxazolone with oxalic acid, d) reduction of the resulting trifluoromethyl ketone-(Aryl) CONH-$\underset{\displaystyle (CH_2)_n\text{-}R^1}{\underset{|}{CH}}$-$(CH_2)_nCOCF_3$ to the corresponding aroylaminotrifluoromethyl carbinol, and e) hydrolysis of this product to a compound of formula VIII wherein Z is CF_3. The instant step e) above is illustrated in Example 14a.

Compounds of formula VIII wherein Z is difluoromethyl,(C_1-C_6)perfluoroalkyl CF_2(C_1-C_5)alkenyl and CF_2(C_1-C_5)alkyl are also prepared by this method. The oxazolone described in the instant step b) above is acylated with difluoroacetic anhydride of the formula [(C_1-C_5)alkenyl$CF_2CO]_2O$ as described by Kolb (ibid., above),

an anhydride of the formula $[(C_1\text{-}C_5)alkylCF_2CO]_2O$ or an anhydride of the formula $[(C_1\text{-}C_6)perfluoroalkylCO]_2O$. These intermediates are converted to compounds of formula VIII by the above-cited steps c) and d) as described by Kolb, and hydrolyzed according to the method of example 14A.

Compounds of formula VIII wherein Z is $CO_2(C_1\text{-}C_5)alkyl$ are prepared as shown in Scheme 4. Alpha-amino acids of formula X or N-protected analogs thereof if not commercially available may be prepared by the Strecker synthesis from an aldehyde of the formula $R^1(CH_2)_nCHO$ or by any of many literature methods, familiar to one skilled in the art, and esterified and protected with a suitable N-protecting group (as described above, eg. BOC or CBZ) to give a compound of formula Xa (R^1 is preferably methyl or ethyl). Many such compounds of formula Xa are also commercially available.

Aldehydes of formula XII are readily prepared from protected α-amino esters of formula Xa by reduction with diisobutylaluminum hydride (DIBAH) or from analogous N-methoxymethylamides by reduction with lithium aluminum hydride (LAH).

Aldehydes of formula XII may be converted to cyanohydrins of formula XIII by treating the aldehyde with a salt of cyanide, preferably potassium or sodium cyanide, in an aqueous solution with a cosolvent such as, tetrahydrofuran, ethyl acetate, or dioxane.

The cyanohydrin of formula XIII so formed can be converted by alcoholysis to a compound of formula VIII wherein Z is $-\overset{O}{\overset{\|}{C}}\text{-}O(C_1\text{-}C_6)$ alkyl. Alcoholysis of a cyanohydrin of formula XIII is typically carried out by treating the cyanohydrin with an alcohol of the formula $alkyl(C_1\text{-}C_6)OH$ with of a proton source, preferably hydrogen chloride gas. The protecting group is then removed (if still present) by one of the methods described above to give a compound of formula VIII. An illustration of the sequence described above wherein Boc-phenylalanine methyl ester is converted to a cyanohydrin of formula XIII is found in U.S. Patent 4,668,769.

An example of the conversion of a cyanohydrin of formula XIII to the corresponding methyl ester of formula VIII with removal of protecting group wherein R^a is BOC is Example 1a. Other examples wherein this cyanohydrin is converted to a variety of low r alkyl esters of formula VIII are found in U.S. Patent 4,814,342.

Compounds of formula VIII wherein Z is $CONR^{12}$ (with R^{13} below)

are prepared from compounds of formula VIII wherein Z is $CO_2(C_1\text{-}C_5)$alkyl by a) protection of the nitrogen group with a protecting group R^e, b) hydrolysis of the ester function with aqueous base as described above, c) coupling of the N-protected hydroxy acid to an amine of the formula $HNR^{12}R^{13}$ or its acid addition salt using standard peptide coupling methods described above (e. g. dicyclohexyl-carbodiimide/HBT). The protecting group R^e is then removed by the methods of scheme 1 to yield the amide of formula VIII wherein Z is $-CONR^{12}R^{13}$. Examples of synthesis of amides of formula VIII by this sequence are reported in U.S. Patent 4,814,342.

Alternatively, amides of formula VIII wherein Z is $-CON-R^{12}$ may be (R^{13} below)

prepared by heating the corresponding esters of formula VIII wherein Z is $CO_2(C_1\text{-}C_5)$alkyl with an excess of an amine of the formula $R^{12}R^{13}NH$ in a solvent such as a lower alcohol at 25-100°C, preferably in a closed system such as a stainless steel bomb. Suitable solvents are methanol, ethanol or isopropyl alcohol.

Compounds of formula VIII wherein Z is $CF_2CONR^{12}R^{13}$ are prepared as outlined in Scheme 5. An aldehyde of formula XII is allowed to react with ethylbromodifluoroacetate in the presence of zinc according to the procedures of Hallinan and Fried (Tetrahedron Lett. 1984, 25, 2301) or Thairivongs et al. (J. Med. Chem. 1986, 29, 2080-7) or with ethyl bromodifluoroacetate, zinc, and titanium tetrachloride (Hoover, U.S. Patent 4,855,303) to yield a compound of formula XIV wherein Z is $CF_2CO_2(C_2H_5)$. The compound of formula XIV is then amidated by mixing with an amine of the formula $R^{12}R^{13}NH$ in a suitable polar, preferably protic, solvent such as ethanol or methanol to give a compound of formula XIV wherein Z is $CF_2CONR^{12}R^{13}$. Removal of the amine protecting group by the methods described in Scheme 1 yields the compound of formula VIII wherein Z is $CF_2CONR^{12}R^{13}$.

Alternatively, the ester of formula XIV may be hydrolyzed to the corresponding acid wherein Z is CF_2CO_2H, and the latter amidated by coupling to an amine of formula $R_{12}R_{13}NH$ by a standard p ptide coupling method to give an amide of formula XIV (Z= $CF_2CONR_{12}R_{13}$), which is then deprotect d to yield a compound of formula VIII. Exampl s of th synth sis of such compounds by these methods can be found in

Example 12a, U.S. Patent 4,855,303, J. Med. Chem. 1992, 35, 2-14, and J. Med. Chem. 1986, 29, 2080-7. By these methods, compounds of formula VIII wherein R_1, n, and Z = $CF_2CONR_{12}R_{13}$ as described herein may be prepared.

Compounds of formula VIII wherein Z is a 2-substituted heterocycle or a benzo-fused 2-substituted heterocycle such as 2-thiazolyl or 2-benzothiazolyl as enumerated above are also prepared as described in Scheme 5. Thus, an aldehyde of formula XII is allowed to react with a 2-metallo heterocycle to form a compound of formula XIV wherein Z is a 2-substituted heterocyclic moiety. Suitable solvents are inert solvents, preferably ether or tetrahydrofuran. The 2-metallo heterocycle is preferably a 2-lithio heterocycle and is obtained by treatment of the parent heterocycle with a suitable organolithium reagent, such as n-butyllithium, methyllithium, sec-butyllithium or tert-butyllithium. 2-Metallo heterocycles may be alternatively prepared by transmetallation of a 2-bromo or 2-iodo heterocycle with an organolithium reagent. Conditions for the formation and use of 2-metallo-heterocyclic reagents are dependent on the particular heterocycle. Methods for the formation of 2-metallo heterocycles are familiar to those skilled in the art. In general, the metallo heterocycle is formed and allowed to react with the aldehyde within 30 minutes at -78°C. Conditions for the formation and reaction of various 2-substituted heterocycles are described in Organic Reactions (Volume 26). Specific applications of this reaction to the synthesis of compounds of formula XIV wherein Z is 2-thiazolyl or 2-benzothiazoyl are Examples 3a and 13c herein. Compounds of formula XIV so formed are then converted to compounds of formula VIII by removing the protecting group by the methods described in Scheme 1, above.

Parent heterocycles having a free NH such as imidazole, tetrazole, or indole are N-protected with an appropriate protecting group, such as 1-ethoxyethyl or trimethylsilylethyl prior to metallation of the heterocycle. Conditions for introduction and removal of these and other protecting groups suitable for this purpose are found in T. Greene "Protecting Groups in Organic Synthesis", Wiley, 1981, N.Y.

Alternatively, compounds of formula VIII wherein Z is substituted or unsubstituted 2-benzoxazolyl or substituted or unsubstituted 2-oxazolyl may be prepared from a cyanohydrin of formula XIII and an appropriate ortho-aminophenol or aminoethanol derivativ , r spectively, by the method of Edwards et. al. (J. Am. Chem. Soc. 1992, 114, 1854-1863).

The synthesis of compounds of formula I wherein Y is $B(OM)_2$ is accomplished by coupling a compound of formula V with an aminoboronic acid ester of the formula $NH_2CHB(OM_2)$. Compounds of the formula I wherein Y is $B(OH)_2$ are synthesized

$(CH_2)_n$-R^1

from compounds of formula I wherein Y is $B(OM)_2$ (e.g. M+M equal to $-C(CH_3)-C(CH_3)_2-$) by reaction of the latter with diethanolamine to yield a diethanolamine ester of formula I wherein Y is $B(OM)_2$ having M+M equal to $-CH_2CH_2NHCH_2CH_2-$, followed by hydrolysis of the diethanolamine ester in the presence of the acid form of an ion exchange resin. An example of the synthesis of an aminoboronic ester of formula XIV (wherein $R^1(CH_2)_n$ is phenylmethyl) and methodology described above for the synthesis of the corresponding compound of formula I is described by Kettner et. al. (J. Biol. Chem. 1984, 259, 15106-15114).

Kinder and Katzellenbogen (J. Med. Chem. 1985, 28, 1917-1920) report that acylamino boronic acids of the formula $RCONHCH(R)B(OH)_2$ are converted to the difluoroboranes of the formula $RCONHCH(R)BF_2$ upon brief exposure to excess hydrogen fluoride (HF) in water and extraction with an organic solvent (such as ethyl acetate). Compounds of formula I wherein Y is BF_2 may be made by the same methods from the analogous compounds wherein Y is $B(OH)_2$.

Compounds of formula XI wherein A is CO; D is NH, O, or $N(C_1-C_5)$alkyl, and R^4 is an N-linked moiety are prepared according to scheme 6. A carboxyl protected α-amino or hydroxy ester of the formula XV, is activated by treatment with a phosgene equivalent such as carbonyldiimidazole and condensed with an amine of the formula R^4-H (or a protected analog thereof, if R^4 contains additional primary or secondary amine functionality) which is generally commercially available or can be readily prepared by literature methods familiar to one skilled in the art. The coupled product is then carboxyl-deprotected as described above in Scheme 2 to give a compound of formula XI. An example of this sequence are Examples 10a and b. Alternatively a compound of formula XV may be directly activated with phosgene or trichloromethyl chloroformate to yield an isocyanate (Lombardino and Gerber, J. Med. Chem. 1964, 7, 97-101), N-carbamoylchloride, or chloroformate derivative wherein D is NH, N-alkyl, or O, respectively, and condens d with amin or protected amine of the formula R^4H to yield a compound f th formula XVI.

Many compounds of formula XI wherein R^4, A, D, and R^3 are as described instantly above are known in the literature and have been prepared by one of these methods. Compounds of formula XI wherein R^3, A, and D are as described above and R^4 contains a protected amine functionality suitable for the synthesis of a compound of formula I possessing a basic nitrogen atom in the R^4 moiety by the strategy outlined above are also known to those skilled in the art. For example, U.S. Patent 4,814,342 describes the synthesis of intermediates of formula XI wherein R^4 is morpholino, 4-oxopiperdino, piperazino, 4-formylpiperazino, 4-methylpiperazino, thiomorpholino or methylamino; A-D is CONH and R^3 is phenylmethyl. Additionally, European Patent 438,233 describes the synthesis of compounds of formula XI wherein R^4 is piperidino, pyrrolidino, or azetidino optionally substituted with amino, alkylamino, dialkylamino, alkylaminodialkyl, or dialkylaminoalkyl, wherein the amine functionality is suitably protected if necessary, and wherein A is >C=O and D is oxygen or NH. Compounds of formula XI so formed can be converted to compounds of formula I by the methods of Schemes 1 and 2. . This methodology as described in EP-438,233 is suitable for the synthesis of other compounds of formula XI and XVI, by those skilled in the art, wherein R^3 is as described herein and D is oxygen or NH, according to Scheme 6, when the corresponding starting material of formula XV and amine or corresponding amine salt of formula R^4-H (or appropriately protected derivative thereof) is employed.

European Patent 476,515 describes the preparation of a compound of formula XVI wherein R^4 is 2-(2-pyridyl)ethyl(methyl)amino, A is carbonyl, D is NH, R_3 is phenylmethyl and R^b is phenylmethyl by the methods of Scheme 6.

Compounds of formula XVI wherein R^4 is a nitrogen-linked substituent or a protected variant thereof, A is carbonyl or sulfonyl, and D is NH, and R^3 and R^b are as described herein may also be prepared according to Scheme 6. An (suitably protected) amine R^4-H is first activated by its conversion to the isocyanate or sulfamoyl chloride (in the case of primary amines), or to the carbamoyl chloride or sulfamoyl chloride (in the case of secondary amines), and this derivative is allowed to react with a compound of formula XV wherein D is NH or N(C_1-C_5 alkyl). The reaction is conducted in an inert solvent such as dichloromethane, chloroform, dimethylformamide, or tetrahydrofuran in the pr senc of a tertiary amine bas , preferably triethylamine or N,N-diisopropylamin . Ros nberg et al. (EP 456,185) describes th synthesis of the compound of formula XVI wherein R^4 is 4-methyl-1-piperazino, A is sulfonyl, D is NH,

and R^3 and R^4 are phenylmethyl by reaction of 1-methylpiperazin-4-yl) sulfonyl chloride (prepared by the method of Matier, J. Med. Chem., 1972, 15, 538) with phenylalanine benzyl ester p-toluenesulfonic acid salt. Compounds of formula XI may also be prepared by reaction of unprotected α-amino acids of formula NH_2-$CH(R^3)CO_2H$ with sulfamoyl chlorides. Wegler et al. (Ann. Chem., 1959, 624, 24-29) describe the synthesis of the compound of formula XI wherein R^4 is morpholino, A is sulfonyl, D is NH, and R^3 is phenylmethyl by this synthetic strategy. These methodologies are adaptable by one skilled in the art to the synthesis of other compounds of formula XVI and XI wherein R^3 is as described herein or a protected variant thereof, A is sulfonyl or carbonyl, D is NH or N(C_1-C_5 alkyl), R^4 is an N-linked substituent or protected variant thereof as described herein.

Compounds of formula XI and XVI wherein R^4-A is alkylcarbonyl, alkoxycarbonyl (C_3-C_7)-cycloalkylcarbonyl, alkylsulfonyl, (C_3-C_7)-cycloalkylsulfonyl, and substituted or appropriately protected substituted variants of these five groupings and D is NH, N-(C_1-C_6)alkyl or oxygen may be prepared by the method of scheme 6 by acylation or sulfonylation of a compound of the formula XVI with the appropriate activated carboxylic acid or sulfonyl chloride derivative. Acylations of this type are accomplished via the acid chloride R^4COCl or by one of the peptide coupling methods described above. Sulfonylation is accomplished in an inert solvent, preferably dichloromethane, in the presence of a tertiary amine base, preferably triethylamine or diisopropylethylamine. Compounds of formula XI and XVI wherein R^4A is substituted or unsubstituted alkoxycarbonyl may be prepared by acylation of a compound of the formula XVI with the appropriate chloroformate or carbonate derivatives.

Compounds of formula XVI and XI wherein A is CO and D is CH_2 are synthesized according to Scheme 7, by coupling of compounds of formula XVII wherein G is OH, A is CO, D is CH_2 and R^b is a suitable carboxyl protecting group to an amine or appropriately protected amine R^4-H. Compounds of formula XVII wherein G is OH, A is CO, D is CH_2 and R^b is a suitable carboxyl protecting group are prepared by literature methods. Plattner et al. (J. Med. Chem. 1988, 31, 2277-2288) describe the synthesis (Scheme V therein) of the compound of formula XVII wherein G is OH, A is CO, D is CH_2, R^3 is ph nylmethyl, and R^b is phenylmethyl in th nantiomeric form preferr d for the R^3-bearing carbon in compounds of formula I herein. Other compounds f formula XVII wherein G is OH, D is CH_2, and R^3 and R^4 are as described

herein may be prepared by this method by one skilled in the art, starting with a suitably carboxyl-activated derivative of the appropriate acid $R^3CH_2CO_2H$ and the amine R^4-H, wherein R^3 and R^4 are as described herein or suitably protected variants thereof. For example, Hoover et. al. (EP-438,233) describes the synthesis by this method of compounds of formula XI wherein A is CO, D is CH_2, R^3 is phenylmethyl and R^4 is 4-oxopiperidino, 2-morpholinoethyl(methyl)amino, 4-dimethylaminopiperidino, 4-pyrrolidinopiperidino, 4-piperidinopiperidino, 4-dimethylaminomethylpiperidino, 4-piperidinomethylpiperidino, and 4-N-t-Boc(methyl)aminomethylpiperidino, and compounds of formula XI wherein A is CO, D is CH_2, R^4 is 4-oxopiperidino, and R^3 is 2-thienylmethyl, 4-iodophenylmethyl, and 3-thienylmethyl. Additionally, European Patent 416,393 describes the synthesis of compound of formula XVI wherein R_4 is 4-trifluoroethylpiperazino, 4-methylpiperazino, and 2-(2-pyridyl)ethyl(methyl)amino by this method. Compounds of formula XI wherein A is CO and D is CH_2 are also prepared by other methods, such as a) Stobbe condensation of a carbonyl compound with a succinic acid diester to give a 2-dihydrosuccinate 1-monoester, b) coupling of the free carboxyl to an amine R^4-H, and c) reduction (e.g., catalytic hydrogenation) of the olefin to a compound of formula XI. Steps a and b of this method are described by Plattner et al. (J. Med. Chem. 1988, 31, 2277-2288) for the synthesis of an olefin which upon hydrogenation would give a compound XI wherein R^4 is morpholino, A is CO, D is CH_2, and R^3 is phenylmethyl. Iizuka et. al. (J. Med. Chem. 1990, 33, 2707-2714) report a closely related method whereby, by varying the carbonyl compound giving rise to R^3 and the amine or protected amine R^4-H, compounds of formula XI wherein A is CO, D is CH_2, R^3 is not an aryl group or tertiary radical, and R^4 is an amine-linked substituent as described herein may be prepared.

European Patent 416,393 describes methods for the synthesis of compounds of formula XI and XVI wherein R^4 is unsaturated heterocyclicethyl(methyl)amino, A is carbonyl, D is CH_2, and R^3 is phenylmethyl, by N-alkylation of a five membered unsaturated heterocycle such as imidazole and pyrazole. One skilled in the art can use this method to prepare other such compounds of formulae XVI and XI by varying the R^3-substituted succinate monoester, and by choosing the appropriate ω-hydroxy-(C_2-C_4)alkyl(C_1-C_5)alkylamine, and by choosing the appropriate heterocycle.

Compounds of formula XVI wherein R^4 is a nitrogen-linked substituent as described above or a protected variant thereof, A is sulfonyl and D is CH_2 may also be

prepared according to Scheme 7, by coupling an amine R^4-H or protected variant thereof with a sulfonyl chloride of the formula XVII wherein G-A is Cl-SO_2-. Certain such compounds of formula XVII and XVI are known in the literature. Rosenberg et al. (EP 456,185) described the preparation of the compound of formula XVI, wherein G is Cl, A is SO_2, D is CH_2, R^3 is phenylmethyl and R^b is methyl or phenylmethyl, and their reaction with selected amines of formula R^4-H including morpholine, N-benzylpiperazine (as a protected form of piperazine) and 1-methylpiperazine. This methodology is adaptable by one skilled in the art to the synthesis of other compounds of formula XVI wherein R^3 is as described herein or a protected variant thereof, A is sulfonyl, D is CH_2 and R^4 is an N-linked substituent or protected variant thereof as described herein.

Compounds of formula XVI wherein R^4 is substituted or unsubstituted alkyl or cycloalkyl, A is sulfonyl, D is CH_2, and R^3 and R^b are as defined herein may be prepared starting from 2-(R^3)-substituted acrylic acid esters by the method described by Buhlmayer et al. (J. Med. Chem. 1988, 31, 1839-1846) wherein a compound of formula XVI wherein R^4 is t-butyl, A is sulfonyl, D is CH_2, R^3 is phenylmethyl, and R^b is ethyl is synthesized by a) conjugate addition of R^4SH (tert-butyl mercaptan) to benzyl 2-benzylacrylate, and b) oxidation of the sulfide to the sulfone. The requisite 2-(R^3)-substituted acrylic acid esters are prepared by the method of Stetter et al. (Synthesis 1979, 29) from 2-(R^3) substituted-malonic diesters or by other methods cited therein. 2-(R^3) substituted-malonic diesters are commercially available or prepared by literature methods.

Compounds of formula XI wherein R^4 is substituted or unsubstituted alkyl or cycloalkyl, A is carbonyl, D is CH_2, and R^3 is as defined herein may be prepared by alkylation of a 2-(R^3) substituted-malonic diester with a bromoketone of formula R^4COCH_2Br, followed by hydrolysis and decarboxylation of this product. Buhlmayer et al. (J. Med. Chem. 1988, 31, 1839-1846) report a method for synthesis of a compound of formula XVI wherein R^4 is t-butyl, A is carbonyl, D is CH_2, and R^3 is phenylmethyl is synthesized by a) alkylation of diethyl benzylmalonate with 1-bromo-3,3-dimethyl-2-propanone b) sodium hydroxide hydrolysis, and c) HCl-induced decarboxylation of the intermediate 2-benzylmalonic acid. Bromoketones of formula R^4COCH_2Br may be prepared, as will be known to one skilled in the art, by many methods such as a) reaction of an activated acid R^4COOH (such as the acid chloride or mixed anhydride)

with diazomethane to give the diazomethyl ketone which is b) treated with anhydrous hydrogen bromide.

European Patent 476,515 describes a method for the preparation of compounds of the formulae XVI and XI wherein R^4 is 2-($R^7CON(CH_3)$)ethyl(methyl)amino, A is carbonyl, D is NH or O, and R^3 is phenylmethyl, wherein R^7 is thiomorpholino, piperidino, or dialkylamino, by acylation of an appropriate methylaminoethyl(methyl)aminocarbonyl-phenylalanine or phenyllactate derivative with R^7COCl. This method may be used by one skilled in the art for the synthesis of other compounds of the formula XVI and XI wherein the precursor containing R^3, the monoprotected (C_1-C_5)alkylamino(C_2-C_4)alkyl(C_1-C_5)alkylamine, and the R^7COCl reagent are appropriately chosen.

Unless indicated otherwise, the pressures of the foregoing reactions are not critical. Generally, the reaction pressures will be about 0.5 to about 2 atmospheres, preferably ambient pressure (i.e., generally at about one atmosphere).

The activity of the active compounds of the present invention as inhibitors of the angiotensin I-cleaving activity of angiotensin I chymase(s) may be determined by studying their ability to inhibit the angiotensin I-cleaving activity of an angiotensin I chymase isolated and semipurified from the heart of the marmoset. Thus, left ventricles were removed from necropsied marmoset monkeys. Tissues were frozen in liquid nitrogen and stored at -70°C. The tissue was thawed and homogenized in 10 volumes (w/v) of 20 mM Tris-HCl, pH 7.4 with a polytron set at 8. The homogenate was centrifuged at 40,000 Xg for 30 min. The pellet was washed twice by homogenization and centrifugation. The final pellet was suspended in 10 volumes of 20 mM Tris-HCl, pH 7.4 with 1% Triton X-100 and 10 mM KCl using a polytron. The homogenate was incubated at 4°C for 1 hr and centrifuged at 40,000 Xg for 30 min. The pellet was homogenized in 20 mM Tris-HCl, pH 8.0 with 1% Triton X-100 and 0.5 M KCl, incubated and centrifuged. The resulting pellet was suspended in 20 mM Tris, HCl, pH 8.0 with 1% Triton X-100 and 2 M KCl, incubated and centrifuged. The supernatant was the source of chymase and was frozen in liquid nitrogen and stored at -70°C. Protein concentration was determined (Bradford, Anal. Biochem. 1976, 72, 248-254). Inhibition of angiotensin I chymases can be determined by an angiotensin-radioreceptor assay. In this assay, angiotensin I is incubated with the chymase in 20 mM Tris-HCl, pH 8.0 with 0.25% Triton X-100 and 0.5 M KCl in a final volume at 100μl. Samples were

incubated at 37°C and a 4°C control was included. The reaction was terminated by the addition of 100 μl of 2 mM phenylmethylsulfonyl chloride (PMSF) in 50 mM Tris-HCl, pH 7.2 with 5 mM $MgCl_2$ and 0.25% bovine serum albumin and placing on ice. The concentration of angiotensin II formed was measured by displacement of radiolabeled angiotensin II from preformed rat liver microsomes saturated with radiolabeled angiotensin II. Rat liver microsomes are a known source of angiotensin II receptors. These microsomes were isolated and purified from the livers of sacrificed rats which were removed and homogenized in 10 volumes of 10 mM Tris-HCl, pH 7.4 with 200 mM sucrose and mM ethylenediaminetetraacetic acid (EDTA) using 10 strokes of a teflon pestle in a glass tube. The homogenate was centrifuged at 3000 Xg for 10 min. The resulting supernatant was centrifuged at 12,000 Xg for 13 minutes. This supernatant was separated and centrifuged at 104,000 Xg for 1 hour. The resulting pellet was suspended in 50 mM Tris-HCl, pH 7.2 with 5 mM $MgCl_2$. The microsomes were assayed for protein (Bradford, ibid) and frozen at -20°C until use. Radiolabeled ^{125}I Sarlle angiotensin II (0.125 nM) was incubated with the rat microsomes (30μg, 100 μl) in 50 mM Tris-HCl, pH 7.2 with 5 mM $MgCl_2$, 1 mM PMSF and 0.25% BSA for 40 min at ambient temperature at a final volume of 200 μl. The reaction was terminated by filtration of the suspension through GF/B filters pretreated with 0.2% PEI and dried. The angiotensin II levels were determined from an angiotensin II standard curve. The IC_{50} of chymase inhibition was defined as the concentration of the inhibitor that inhibited 50% of the enzyme activity and was determined by increasing concentration of inhibitor.

The colorimetric assay is a less time intense alternative method for measuring the inhibitory activity of the compounds of this invention against the angiotensin I cleaving action of chymases. In this assay, the experimental sample is prepared by mixing inhibitor (90 μl, in 10% methanol) with enzyme, (90 μl, in 20 mM Tris, pH 8.0, 2 M KCl, 1% Triton X-100 (47 μg/well)) and is pre-incubated at 37°C for 20 minutes. A control sample of the enzyme, (90 μl, in 20 mM Tris, pH 8.0, 2 M KCl, 1% Triton X-100 (47 μg/well)) is separately prepared. To each of these samples is added a solution of a peptidyl para nitroanilide substrate (N-succinoyl-Phe-Val-Pro-Phe-p-Nitroanilide) (180 μl volume of 400 μM) in 30 mM Tris, pH 8.0 (200 μM final concentration). The final buffer c ncentration is 20 mM Tris, pH 8.0 with 0.5 M KCl and 0.25% Triton X-100. Cleavage of the para nitroanilide moiety by the chymas produces a color change. As the reaction f xp rim ntal and control sampl s ar incubated at 37°C for 3 hours,

the color change is continuously recorded by the increase in absorbance at 410 nanometers (NM). The rate reaction is expressed as mOD/minutes. The IC50 of the chymase inhibitors was defined as the concentration of the inhibitor that inhibited 50% of the enzyme activity and was determined by increasing concentration of inhibitor.

The following examples illustrate the invention but are not to be construed as limiting the same. All melting points are uncorrected. In the Examples, "boc" refers to t-butoxycarbonyl and "diboc" to di-t-butoxy-carbonyl.

The active compounds of the present invention can be administered as antihypertensive agents, agents for the treatment of congestive heart failure, cardiac and vascular hypertrophy including left ventricular hypertrophy and diabetic and non-diabetic renal disease by either the oral or parental routes of administration, with the former being preferred for reasons of patient convenience and comfort. In general, these compounds are normally administered orally in dosages ranging from about 0.1 to about 50 mg per kg of body weight per day, preferably about 0.1 to about 20 mg per kg of body weight per day, and about 0.05 mg to about 10 mg per kg of body weight per day, preferably about 0.05 to about 2 mg per kg of body weight per day, when given parenterally; variations will necessarily occur depending upon the condition of the subject being treated and the particular compound being administered. Typically, treatment is commenced at a low daily dosage and increased by the physician only if necessary. It is to be noted that these compounds may be administered in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages.

The active compounds of the present invention can be orally administered in a wide variety of different dosage forms, i.e., they may be formulated with various pharmaceutically acceptable inert carrier in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, elixirs, syrups and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the active compounds of the pr sent invention ar present in such oral dosage forms at concentration levels ranging

from about 0.5% to about 90% by weight of the total composition, in amounts which are sufficient to provide the desired unit dosages.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch (preferably potato or tapioca starch), alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc and compositions of a similar type may also be employed. Lactose or milk sugar as well as high molecular weight polyethylene glycols may be employed as fillers in soft and hard-filled gelatin capsules. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying agents and/or solvents such as water, ethanol, propylene glycol, glycerin or combinations thereof.

One or more other active compounds may be added to the formulations described above to provide formulations for combination therapy. Such compounds include antihypertensives such as diuretics, beta-adrenergic blocking agents, central nervous system-acting agents, adrenergic neuron blocking agents, vasodilators, renin inhibitors, angiotensin II antagonists, and angiotensin I converting enzyme inhibitors. A preferred antihypertensive agent for administration together with a compound of the present invention is a diuretic.

EXAMPLES

Amicon silica 30 μM, 60 Å pore size, was used for column chromatography.

Melting points were taken on a Buchi 510 apparatus and are uncorrected. Proton and carbon NMR spectra were recorded on a Varian XL-300, Bruker AM-300, or Bruker AM-500 at 25°C. Chemical shifts are expressed in parts per million downfield from trimethylsilane. Liquid secondary ion mass spectra (LSIMS) were obtained on a Kratos Concept-1S high resolution spectrometer using cesium ion bombardment on sample dissolved in a 1:5 mixture of dithioerythritol and dithiothreitol in methanol. For initial sample dissolution chloroform, methanol, or ethanol were employed. Reported data are sums of 3-20 scans calibrated against cesium iodide. FAB-MS spectra were obtained on a Kratos MS-80RFA spectrometer operating in the FAB mode on sample dissolved in a thioglycerol matrix. Thin layer chromatography (TLC) analyses were

performed using E. Merck Kieselgel 60 F254 silica plates visualized (after elution with the indicated solvent(s)) by staining with 15% ethanolic phosphomolybdic acid and heating on a hot plate. HPLC was performed with 214 nm detection on a (system A) 150 mm Waters Novapak C18 column eluted at 0.8 ml/min, or (System B) 250 mm Rainin Microsorb C18 column eluted at 1.0 ml/min by a two-pump/mixer system supplying the indicated mixture (v:v) of acetonitrile and aqueous pH 2.1 (H_3PO_4) 0.1 M KH_2PO_4 respectively. The terms "concentrated" and "coevaporated" refer to removal of solvent at water aspirator pressure on a rotary evaporator with a bath temperature of less than 40°C. Organic solutions were dried over magnesium sulfate unless specified otherwise.

General Procedure A (Peptide Coupling Using DEC)

A solution of the primary amine (0.2-0.5 M, 1.0 equivalent) in dichloromethane (or a primary amine hydrochloride and 1.0-1.3 equivalents of triethylamine) is treated sequentially with the carboxylic acid coupling partner (1.0-1.2 equivalents), hydroxybenzotriazole hydrate (HBT) (1.5-1.8 equivalents), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC) (1.0-1.2 equivalents, stoichiometrically equivalent to the quantity of carboxylic acid) and the mixture is stirred overnight in an ice bath. The ice bath is allowed to warm, thus the reaction mixture is typically held at 0-20°C for 4-6 hours and 20-25°C for the remaining period. The mixture is diluted with ethyl acetate or other solvent as specified, and the resulting mixture was washed twice with 1N NaOH, twice with 1N HCl, once with brine, then dried over magnesium sulfate ($MgSO_4$), and concentrated to give the crude product which is purified as specified. The carboxylic acid component can be used as the dicyclohexylamine salt in coupling to the primary amine or hydrochloride of the latter; in this case no triethylamine is employed.

General Procedure B. (HCl-Dioxane Cleavage of a t-Boc-Protected Amine)

A cold (0-10°C) solution of 4N HCl-dioxane is added by syringe to the solid t-Boc amine (typically about 10 mL per gram amine) and the resulting solution is stirred at 25°C for 0.25-2 hours. The time required for complete disappearance of the starting material to a more polar product as judged by TLC. The resulting solution or suspension is then concentrated, and the residue coevaporated several times with added ether, and then dried in vacuo. If specified, the solid hydrochloride is washed further with solvent.

General Procedure C. Periodinane Oxidation of a peptidyl α-Hydroxyester, Difluorostatine, or Trifluoromethyl Carbinol to the Corresponding Ketone.

The procedure of Burkhart, et al. (Tetrahedron Lett. 1988, 29, 3433-3436) for the oxidation of α-hydroxyesters by the Dess-Martin periodinane (J. Org. Chem. 1983, 48, 4155) was employed with several slight modifications (use of 4 equiv periodinane reagent and longer reaction times, and variation in extraction solvent). Thus, a solution of the peptidyl α-hydroxy ester (e.g., 1 mmol) in dry dichloromethane (about 5 mL) was treated with the above referenced periodinane (4 equiv), and the reaction mixture was stirred overnight (about 16 hours) at 25°C. If the reaction was not complete (TLC), additional periodinane was added as specified. When complete reaction was verified the mixture was diluted with the specified extraction solvent and water (20-100 mL each/mmol substrate), $Na_2S_2O_3 \cdot 5H_2O$ (1.3-3 g/mmol substrate) and $NaHCO_3$ (2.5-3 g/mmol substrate) were added, and the resulting solution stirred 1 to 2 hours or until both layers clarified. The separated organic layer was washed with aqueous $NaHCO_3$, brine, and combined with one extract (same solvent) of the separated aqueous layers. The combined organic layers were dried ($MgSO_4$), concentrated, and the residue chromatographed on silica eluted with the specified solvent mixture.

Example 1

N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. Methyl-3(S),2(R)-3-amino-2-hydroxy-4-phenylbutanoate

3(S),3(R)-N-[(1,1-dimethylethoxy)carbonyl]-3-amino-2-hydroxy-4-phenylbutyronitrile (U.S. Patent 4,668,769, 9.13 g, 33.0 mmol) was added in several portions at 0°C to a stirred solution of anhydrous hydrogen chloride (60 g) in absolute methanol (250 mL). The resulting solution was warmed to 25°C for 5 minutes and the flask was sealed with a plastic stopper and placed behind a safety shield (Caution!). After 63 hours at 25°C, slight pressure was relieved by piercing the stopper with a syringe needle, and the mixture was concentrated and dried in vacuo. The resulting solid (9.94 g) was suspended in saturated aqueous $NaHCO_3$ (about 250 mL) and the mixture extracted with chloroform (10 times 50 mL). The extracts were dried ($MgSO_4$) and concentrated. The residue (6.22 g) was recrystallized from 1:2 ethyl acetate-hexanes (120 mL, by dissolving in hot ethyl acetate and adding hexanes at reflux). The solid was collected at 0°C, washed with chilled 1:2 ethyl acetate-hexanes, and dried in vacuo at 56°C (5.31 g, 77%): m.p. 106-107°C. ^{1}H NMR ($CDCl_3$) δ 1.5 (br, 3H), 2.73 (dd, 1H, J = 8.3, 13.3 Hz), 2.92 (dd, 1H, J = 6.6, 13.3 Hz), 3.37 (m, 1H), 3.79 (s, 3H), 4.08 (d, 1H), 7.2-7.35 (m, 5H). Anal. Calcd for ($C_{11}H_{15}NO_3$) C, 63.14; H, 7.23; N, 6.69. Found: C, 63.16; H, 7.01; N, 6.61.

B. N^1-[(1,1-dimethylethoxy)carbonyl]-N^a-[2(R)-hydroxy-3-methoxy-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The following illustrates a specific application of General Procedure A. A solution of the product of Example 1 (3.81 g, 18.2 mmol) in dichloromethane (125 mL) was treated sequentially at 0°C with N-t-butoxycarbonyl-L-proline (4.30 g, 20.0 mmol), 1-hydroxybenzotriazole hydrate (HBT, 4.20 g, 27.3 mmol), and 1-(3-dimethylaminopropyl) ethylcarbodiimide hydrochloride (DEC, 3.83 g, 20.0 mmol). The mixture was stirred 40 hours during which time the temperature rose to 25°C. Dichloromethane (200 mL) was added and the resulting solution washed with 2N NaOH (2 times 70 mL), 1N HCl (70 mL), and then dried ($MgSO_4$) and concentrated. The residu (6.0 g) was recrystallized from 1:1 chloroform-hexanes giving 5.75 g (78%) of a colorless solid, m.p. 167-168.5°C. ^{1}H NMR ($CDCl_3$) δ 1.25 (m, ca. 1H), 1.48 (s, 9H), 1.6-2.0 (m, ca. 3H), 2.13 (br, ca. 0.5 H), 2.86 (dd, 1H, J = 8.3, 13.7 Hz), 2.96 (m, 1H),

3.18 (m, exchanges with D_2O), 3.3-3.4 (m, 2H), 3.76 (s, 3H), 4.11 (d, 1H, J = 5.1 Hz, collapses to s with D_2O), 4.18 (br, 1H), 4.58 (br, 1H), 6.23 (br, ca. 0.5 H), 7.02 (br, ca. 0.5H), 7.15-7.35 (m, 5-6H). LSIMS m/e (rel. intensity) 407 (M^++H, 70), 351 (20), 307 (100). Anal. Calcd for ($C_{21}H_{30}N_2O_6 \bullet 0.5H_2O$) C, 60.70; H, 7.52; N, 6.74. Found: C, 60.92; H, 7.12; N, 6.43.

C. N-[2(R)-hydroxy-3-methoxy-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide Hydrochloride

The following preparation illustrates a specific application of Procedure B. A 5°C solution of anhydrous hydrogen chloride in p-dioxane (30 mL of 4M) was added in one portion to the product of the preceding example (3.24 g, 7.97 mmol) and the resulting solution was warmed to 25°C. After 30 minutes, the mixture was concentrated, and the residue dried in vacuo and triturated with ether (3 x 6 mL). The resulting colorless solid was dried in vacuo at 56°C for 1.5 hours (2.82 g, 103%). ^1H NMR (D_2O) 1.8-2.1 (m, 3H), 2.38 (m, 1H), 2.85 (dd, 1H, J = 9.9, 13.8 Hz), 3.02 (dd, 1H, J = 5.8, 13.9 Hz), 3.31 (m, 2H), 3.68 (s, 3H), 4.15 (dd, 1H, J = 5.8, 8.6 Hz), 4.41 (d, 1H, J = 2.0 Hz), 4.53 (ddd, 1H, J = 2.0, 5.8, 9.9 Hz), 7.2-7.4 (m, 5H). LSIMS 307 (M^++H, 100%).

D. N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

According to general procedure A, the product of Example 1C (250 mg) was coupled to N-(1,1-dimethylethoxy)carbonyl-L-phenylalanine (1.1 equiv) giving 350 mg of crude product which was chromatographed on silica eluted with ethyl acetate-hexanes giving the title substance (306 mg, 76%). Anal. Calcd for ($C_{30}H_{39}N_3O_7 \bullet 0.5H_2O$): C, 64.04; H, 7.17; N, 7.47. Found: C, 64.09; H, 7.14; N, 7.22.

E. N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The following preparation illustrates an application of General Procedure C except that less periodinane was initially added. Dess-Martin periodinane (265 mg, 0.61 mmol) was added to a solution of the product of the preceding example (168 mg, 0.30 mmol) in dichloromethane (10 mL) and the mixture was stirred 16 hours at 25°C. Additional periodinane (265 mg, 0.61 mmol) was added and the mixture was stirred at 25°C another 72 h urs. Th mixtur was diluted with ethyl acetate (30 mL) and a s lution of $NaHCO_3$ (0.70 g) and $Na_2S_2O_3 \bullet 5H_2O$ (2.2 g) was added, and the mixtur

was stirred until both layers became clear. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The combined aqueous layers were extracted once with ethyl acetate. The combined organic layers were dried ($MgSO_4$), and concentrated to yield 144 mg of a colorless foam which was chromatographed on 5 g silica packed in 0.5:100 ethanol-dichloromethane and eluted with 50 mL portions of 1:100, 2:100, and 4:100 ethanol-dichloromethane to yield the title substance (70 mg, 42%) as a colorless powder, (TLC Rf 0.55, ethyl acetate-silica).

LSIMS 552 (30%, MH^+), 496 (10%), 452 (100%).

Example 2

N-[(1,1-dimethylethoxy)carbonyl]-L-histidyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. $N^{\alpha}N^{\tau}$-Bis[(1,1-dimethylethoxy)carbonyl]-L-histidyl-L-proline phenylmethyl ester

According to General Procedure A, L-proline phenylmethyl ester hydrochloride (8.0 g) was coupled to $N^{\alpha}N^{\tau}$-bis-[(1,1-dimethylethoxy)carbonyl]-L-histidine (11.8 g) and the crude product (11.1 g, oil) was chromatographed on 200 g silica eluted with 2:1 ethyl acetate-hexanes followed by ethyl acetate. 3.1 g of the less polar product was isolated and identified by NMR as Boc-Pro-OBn; the more polar substance, a colorless foam (6.89 g, 39%) was identified as the title compound:

LSIMS 543 (75%, MH^+), 487 (30%), 443 (25%), 387 (40%), 343 (75%). Anal. Calcd. for ($C_{28}H_{38}N_4O_7 \bullet O.5H_2O$): C, 60.96; H, 7.12; N, 10.16. Found: C, 61.02; H, 6.86; N, 10.08.

B. $N^{\alpha}N^{\tau}$-Bis[(1,1-dimethylethoxy)carbonyl]-L-histidyl-L-proline

A solution of the product of the preceding example (1.0 g, 1.84 mmol) in ethyl acetate was shaken with 20% $Pd(OH)_2/C$ under 50 p.s.i. hydrogen pressure for 3 hours. The mixture was filtered through Supercel (trademark) and the cake washed with ethyl acetate. The filtrate was concentrated giving 0.87 g of a colorless foam, (TLC R_f 0.5 in 18/2/1 $HCCl_3$/Ethanol/HOAc).

C. $N^{\alpha}N^{\tau}$-Bis[(1,1-dimethylethoxy)carbonyl]-L-histidyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

2-Ethoxy-1- thoxycarbonyl-1,2-dihydroquinoline (EEDQ, 247 mg, 1.00 mmol) was added to a solution of th product of th pr ceding Example (450 mg, 1.00 mmol) and th product of Exampl 1a (210 mg) in dichloromethan (5 mL) and the resulting

solution was allowed to stir at 25°C for 48 hours. The reaction mixture was diluted with 100 mL ethyl acetate and the resulting solution was washed with 10% aqueous citric acid (2 x 40 mL), saturated aqueous $NaHCO_3$ (2 x 40 mL), dried ($MgSO_4$) and concentrated to yield the crude product as a colorless foam (602 mg, 94%), (TLC R_f 0.19 in ethyl acetate). LSIMS 644 (MH^+, 20%), 544 (100%).

D. N$^{\alpha}$N$^{\tau}$-Bis[(1,1-dimethylethoxy)carbonyl]-L-histidyl-N-[2,3-dioxo-3-methoxy-1(S)-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C, except that only 2 equiv of periodinane was used, and that chloroform, rather than ethyl acetate, was used as the extraction solvent. The product of the preceding example (642 mg) was converted to the title substance (530 mg, 83%) which was not further purified. (TLC R_f 0.22, ethyl acetate).

E. N$^{\alpha}$-[(1,1-dimethylethoxy)carbonyl]-L-histidyl-N-[2,3-dioxo-3-methoxy-1(S)-(phenylmethyl)propyl]-L-prolinamide

The product of the preceding example (151 mg, 0.236 mmol) was dissolved in acetic acid (1 mL) and water (1 mL) for 18 hours at 25°C. Concentration and drying gave 139 mg of solid which was dissolved in a mixture of methanol (2 mL) and 0.5 mL saturated aqueous $NaHCO_3$. Silica (3 g) was added and the solvent was removed in vacuo. The solid was added to the top of a 10 g silica column which was eluted with 100 mL portions of 1% and 2% ethanol-dichloromethane, and 50 mL portions of 4%, 8% and 20% ethanol-dichloromethane to yield the title substance (82 mg, 64%), (TLC R_f 0.55, 9:1 dichloromethane-ethanol containing aq. NH_4OH).

LSIMS 696 (MH^+ +dithiothreitol, 100%), 542 (MH^+, 50%).

Example 3

N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2-(2-thiazolyl)-2-oxo-1-(phenylmethyl)ethyl]L-prolinamide

A. 1(R,S), 2(S)-1-(2-thiazolyl)-2-[N-[(1,1-dimethylethoxy)carbonyl]amino]-3-phenyl-1-propanol

N-Butyllithium in hexane (7.1 mL, 17.7 mmol) was added dropwise to a -78°C solution of thiazole (2.1 g, 17.7 mmol) in tetrahydrofuran (20 mL) and the resulting mixture was stirred at -78°C for 30 minutes. A solution of 2-[N-(1,1-dimethylethoxy)carbonyl]amino]-3-phenyl-1-propanal was added and the mixture was stirred for 45 minutes at -78°C. The mixture was warmed to 0°C and treated with

saturated aqueous NH_4Cl. Ethyl acetate was added and the resulting solution was washed twice with water, brine, dried ($MgSO_4$) and concentrated giving 2.2 g of crude product which was purified on silica eluted with ethyl acetate-hexanes giving the title product (580 mg, 22%). LSIMS 335 (MH^+, 100%), 279 (50%).

B. 1(R,S), 2(S)-1-(2-thiazolyl)-2-amino-3-phenyl-1-propanol hydrochloride

According to Procedure B, the product of the preceding Example (546 mg) was converted to the title hydrochlorides (500 mg), TLC Rf 0.75 and 0. 72 (18/2/1 CH_2Cl_2-EtOH-NH_4OH). LSIMS 235 (100%, MH^+).

C. N(morpholino-1-carbonyl)-L-phenylalanyl-N[2-(2-thiazolyl)-1(R,S)-hydroxy-1-(S)-phenylmethyl)ethyl]-L-prolinamide

The product of the preceding Example (200 mg) was coupled to the product of Example 13B (free acid, 304 mg) using General Procedure A, giving 265 mg of crude product which was purified on silica eluting with a gradient (1-16%) of ethanol in dichloromethane. Yield, 194 mg, 43%, TLC Rf 0.73 (9:1 dichloromethane-ethanol). LSIMS 592 (MH^+, 40%), 309 (45%).

D. N-(morpholino 1-carbonyl)-L-phenylalanyl-N-[2-(2-thiazolyl)-2-oxo-1-(phenylmethyl)ethyl]-L-prolinamide

According to General Procedure C, the product of the preceding Example (194 mg) was treated with the periodinane, and the crude product (133 mg), isolated by ethyl acetate extraction, was purified on silica eluted with ethyl acetate giving the title product (76 mg, 42%), TLC Rf 0.85 in 18/2/1 CH_2Cl_2-EtOH-NH_4OH. LSIMS 590 (MH^+, 90%), 330 (70%).

Example 4

N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 1C (250 mg) was coupled to Boc-L-leucine to yield 346 mg of crude product which was purified on silica eluting with ethyl acetate-hexanes and ethyl acetate to yield th title substance (303 mg, 80%).

LSIMS 520 (MH^+, 95%), 420 (100%).

Anal. ($C_{27}H_{41}N_3O_7 \cdot 0.5\ H_2O$) C, H, N, wer within 0.4% of th calculat d value.

B. N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C, with the following exception: 200 mg of the product of the preceding Example was treated with a total of 6 equiv of the periodinane which was added in 2 equiv portions over 7 days, until the reaction was complete by HPLC. Ethyl acetate was employed in the workup and the crude product (164 mg) was chromatographed on silica eluted with a gradient of 0.5-4% ethanol in dichloromethane to yield the title substance (148 mg).

(TLC R_f 0.52, ethyl acetate).

LSIMS 672 (20%, MH^++matrix), 564 (35%, $MH^+ + C_2H_5OH$), 518 (50%, MH^+), 462 (35%), 418 (100%).

Anal. ($C_{27}H_{39}N_3O_7 \cdot 0.6\ H_2O$) C, H, N were within 0.4% of the calculated value.

Example 5

N-[(1,1-dimethylethoxy)carbonyl]-3-(4-thiazolyl)-L-alanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. N-[(1,1-dimethylethoxy)carbonyl]-3-(4-thiazolyl)-L-alanyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 1C (266 mg)was coupled to Boc-3-(4-thiazolyl)-L-alanine) (200 mg) and the crude product (370 mg) purified by chromatography on silica eluted with ethyl acetate-hexanes, ethyl acetate, and ethanol-ethyl acetate to yield the title substance (195 mg, 46%), (TLC R_f 0.25, ethyl acetate).

LSIMS 561 (MH^+, 100%).

B. N-[(1,1-dimethylethoxy)carbonyl]-3-(4-thiazolyl)-L-alanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (190 mg) was oxidized with the periodinane (ethyl acetate used for extraction) to yield 183 mg of crude product which was purified on silica eluted with ethyl acetate-hexanes followed by ethyl acetate, to yi ld 136 mg (72%) of the title substance (TLC R_f 0.35 in ethyl acetate).

^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.8 (m, 3H), 2.12 (m, 1H), 2.9 (m, 1H), 3.00 (dd, 1H, J = 9.6, 14.1 Hz), 3.12 (m, 2H), 3.35 (dd, 1H, J = 14.2 Hz), 3.40 (m, 1H), 3.86 (s,

3H), 4.58 (m, 1H), 4.60 (dd, 1H), 5.11 (m, 2H), 5.48 (m, 1H), 7.08 (s, 1H), 7.19 (d, 2H), 7.2-7.35 (m, 3-4H), 8.62 (s, 1H).

LSIMS 713 ($MH^+ + C_4H_{10}O_2S_2$, 40%), 559 (MH^+, 90%), 127 (100%).

Anal. ($C_{27}H_{34}N_4O_7S \cdot 9/8\ H_2O$) C, H, N were with 0.4% of the calculated value.

Example 6

N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 1C (250 mg) was coupled to Boc-L-alanine (141 mg) to yield 280 mg of crude product which was purified on silica eluted with ethyl acetate-hexanes to yield the title product (191 mg, 56%), (TLC R_f 0.29 in ethyl acetate).

Anal. Calcd for $C_{24}H_{35}N_3O_7 \cdot 0.25\ H_2O$: C, 59.79, H, 7.42; N, 8.71. Found: C, 59.82; H, 7.66; N, 8.46.

B. N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (130 mg) was treated with periodinane (4.6 equiv) and the crude product, isolated by chloroform extraction, was purified on silica eluted with ethyl acetate-hexanes followed by ethyl acetate, to yield 86 mg (67%) of the title substance (TLC R_f 0.34 in ethyl acetate).

^1H NMR ($CDCl_3$ δ 1.13 (d, 3H, J = 6.9 Hz), 1.43 (s, 9H), 1.85 (m, 1H), 1.95 (m, 2H), 2.32 (m, 1H), 2.97 (dd, 1H, J = 8.0, 14.2 Hz), 3.23 (dd, 1H, J = 5.6, 14.2 Hz) 3.38 (m, 1H), 3.58 (m, 1H), 3.85 (s, 9H), 4.38 (dq, 1H), 4.57 (dd, 1H), 5.27 (m, 2H), 7.14 (dd, 1H), 7.2-7.4 (m, 3-4H). A set of resonances presumed due to a minor rotamer (ca. 10%) were also observed: δ 3.8 (s), 4.96 (m), 4.22 (m).

LSIMS 476 (MH^+, 50%), 420 (50%), 376 (100%).

Anal. Calcd for $C_{24}H_{33}N_3O_7$: C, 60.62; H, 6.99; N, 8.84. Found: C, 60.55; H, 7.08; N, 8.84.

Example 7

N-[(1,1-dimethylethoxy)carbonyl]-L-prolyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. N-[(1,1-dimethylethoxy)carbonyl]-L-prolyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 1C (250 mg) was coupled to Boc-L-proline (173 mg) to yield 291 mg of crude product which was purified on silica eluted with ethyl acetate-hexanes followed by ethyl acetate to yield 245 mg (67%) of the title product.

Anal. Calcd for $C_{26}H_{37}N_3O_7 \bullet 0.5\ H_2O$: C, 60.91; H, 7.27; N, 8.20. Found: C, 61.03; H, 7.63; N, 8.04.

B. N-[(1,1-dimethylethoxy)carbonyl]-L-prolyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (204 mg) was treated with periodinane and the crude product, isolated by chloroform extraction, was purified on silica eluted with ethyl acetate-hexanes, to yield 172 mg (85%) of the title substance, (TLC R_f 0.24 in ethyl acetate).

LSIMS 502 (MH^+, 22%), 402 (100%).

Anal. Calcd for $C_{26}H_{35}N_3O_7 \bullet 1.5\ H_2O$; C, 59.07; H, 7.24; N, 7.95. Found: C, 58.85; H, 6.85; N, 7.70.

Example 8

N-[(1,1-dimethyethoxy)carbonyl]-L-valyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. N-[(1,1-dimethyethoxy)carbonyl]-L-valyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 1C (250 mg) was coupled to Boc-L-valine (174 mg) to yield 276 mg of crude product which was purified on silica eluted with ethyl acetate-hexanes to yield 189 mg (51%) of the title product.

LSIMS 506 (M^++H, 45%), 450 (10%), 406 (100%), 307 (70%). Anal. Calcd for $C_{26}H_{39}N_3O_7$: C, 61.76; H, 7.77; N, 8.31. Found: C, 62.23; H, 7.43; N, 8.25.

B. N-[(1,1-dimethylethoxy)carbonyl]-L-valyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1-(phenylmethyl)propyl]-L-prolinamide

According to General Procedure C, the product of the preceding example (140 mg) was oxidized and the crude product (137 mg), isolated by chloroform extraction, was purified on silica eluted with ethyl acetate-hexanes giving 107 mg (77%) of the title product, TLC Rf 0.n 1:1 ethyl acetate-hexanes.

^{1}H NMR ($CDCl_3$) 0.82 (d, 3H, J = 6.7 Hz), 0.83 (d, 3H, J = 6.7 Hz), 1.42 (s, 9H), 1.83 (m, 2H), 1.94 (m, 2H), 2.29 (m, 1H), 3.02 (dd, 1H, J = 7.2, 14.0 Hz), 3.18 (dd, 1H, J = 6.1, 14.0 Hz), 3.52 (m, 1H), 3.68 (m, 1H), 3.82 (s, 3H), 4.21 (dd, 1H, J = 6.3, 9.2 Hz), 4.56 (dd, 1H, J = ca. 8, ca. 3 Hz), 5.14 (d, 1H, J = 9.5 Hz), 5.30 (dt, 1H, J = 6.3 6.9 hz), 7.14 (m, 2H), 7.2-7.4 (m, ca. 3-4H). A set of resonances presumed due to a minor rotamer (ca. 10%) were also observed: d 0.99 (d, J = 6.7 Hz), 1.00 (d, J = 6.7 Hz), 3.84 (s), 3.91 (m).

LSIMS 504 (M^++H, 30%), 448 (30%), 404 (100%), 305 (75%).

Anal. Calcd for $C_{26}H_{37}N_3O_7 \bullet 0.5\ H_2O$: C, 61.45; H, 7.34; N, 8.27. Found: C, 61.56; H, 7.61; N, 8.16.

Example 9

N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as Procedure A. The product of Example 1C (500 mg) was coupled to N-(morpholino-1-carbonyl)-L-phenylalanine (USP 4,814,342, 446 mg) and the crude product (828 mg) was purified by chromatography on silica and eluted with 1%-32% ethanol in dichloromethane to yield the title substance (186 mg, 22%), (TLC R_f 0.41 in 5% ethanol-dichloromethane).

LSIMS 567 (MH^+, 100%), 442 (60%), 307 (70%).

B. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as G neral Pr cedur C. Th product of th prec ding Example (168 mg) was tr ated with periodinane and the crude product (146 mg) was isolated by xtraction using thyl

acetate and was purified on silica eluted with 1-32% ethanol in dichloromethane to yield the title substance (107 mg, 63%).

Anal. Calcd for $C_{30}H_{36}N_4O_7 \cdot 0.5\ H_2O$: C, 62.81; H, 6.50; N, 9.77. Found: C, 62.96; H, 6.45; N, 9.88.

Example 10

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

A. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanine benzyl ester

L-Phenylalanine benzyl ester p-toluenesulfonate (420 g, 0.982 mol) was added to a stirred mixture of 1N NaOH (1.5 L) and dichloromethane (0.5 L) at 25°C. After the solid dissolved the organic layer was separated, dried over $MgSO_4$, and added over 1 hour to a stirred 0-5°C slurry of imidazole (135 g, 1.96 mol, 2.0 equiv) and carbonyldiimidazole (175 g, 1.08 mol) in dichloromethane (1.6 L). The resulting clear solution was warmed rapidly to 25°C and stirred 1 hour at this temperature. 4-Piperidone hydrate hydrochloride (200 g, 1.28 mol, 1.3 equiv) and triethylamine (178 mL, 1.28 mol, 1.3 equiv) were added sequentially, each in one portion, and the mixture was stirred overnight at 25°C. The mixture was washed with 1 N HCl (3 x 800 mL), and the resulting organic layer (partially emulsified) was diluted with dichloromethane (2 L) and divided into two equal portions. Each half was washed with 2N HCl (0.6 L). The combined aqueous layers were washed with dichloromethane (1.6 L), and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated to a viscous yellow oil which was coevaporated twice with added ether to give an off-white solid (352 g, 94%). This material was dissolved in hot 2:1 (v:v) ethyl acetate-hexanes (1.2 L) and the resulting near-solution was filtered through a cotton plug. Crystallization rapidly ensued as the mixture was allowed to stand undisturbed for 1 hour. After the mixture was chilled in an ice bath the mass was filtered, washed with cold 2:1 ethyl acetate-hexanes and hexanes and dried to yield 260 g (70%) of a colorless crystalline solid, homogeneous by TLC (R_f 0.27 in 2:1 ethyl acetate-hexanes) and HPLC (2.56 min in 70:30 MeCN-pH 2.1 phosphate): m.p. 104-107°C; NMR ($CDCl_3$, ppm) 2.39 (m, 4H), 3.11 (dd, A of ABX, 1H, J = 5.7, 13.8 Hz), 3.16 (B of ABX, 1H, J = 5.7; 13.8 Hz), 3.61 (m, 4H), 4.85 (˜dt, 1H, J = 7.6, 5.8 Hz), 4.97 (d, 1H, J = 7.6 Hz), 5.11 (A of AB, 1H,

J = 12.1 Hz), 5.21 (B of AB, 1H, J = 12.1 Hz), 7.00 (dd, 2H, J = 2.5, 5.9 Hz), 7.18-7.37 (m, 8H); IR ($CHCl_3$) 3435, 2990, 1731, 1651, 1496, 1401, 1176, 982 cm^{-1}. Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

B. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanine

The product of the preceding example (115 g, 0.605 mol) was added to 12 g 10% Pd/C in methanol (900 mL) and acetic acid (100 mL), and the resulting mixture was shaken under 30 p.s.i. hydrogen for 35 minutes and then filtered through washed Celite which was washed well with methanol. The filtrates and washings were combined and concentrated in vacuo leaving a viscous yellow oil which was coevaporated twice with added toluene and twice with added ether. The residue was dissolved in chloroform (500 mL) and the resulting solution was washed with water (4 x 250 mL), brine, dried over $MgSO_4$, and stirred with 7 g of decolorizing carbon (Darco, trademark) G-60 at 25°C for 20 minutes. The mixture was filtered through diatomaceous earth (Supercel, trademark) and the filtrates concentrated in vacuo and dried at 0.2 mm and 25°C for 16 hours leaving a colorless foam which was pulverized to an off-white powder (72.4 g, 83%). An impurity (6% by RP-HPLC) was present which was identified by NMR as the corresponding dimethyl ketal. This material (63.7 g)was dissolved in tetrahydrofuran (190 mL) and aqueous 1N HCl (19 mL) at 25°C. After 2.5 hours at 25°C and 16 hours at 0°C the mixture was concentrated to near dryness, the residue dissolved in ethyl acetate (700 mL) and the resulting solution was washed twice with 1N HCl. The aqueous extracts were combined, extracted twice with ethyl acetate, and the combined organic layers dried ($MgSO_4$) and concentrated. The colorless foam was pulverized and dried in vacuo (60.1 g, 78% projected overall yield). ^1H NMR (300 mHz, $CDCl_3$) δ 2.33 (m, 4H), 3.02 (dd, 2H, J = 7.2, 13.8 Hz), 3.21 (dd, 2H, J = 4.9, 13.8 Hz), 3.55 (m, 4H), 4.69 (dt, 1H, J = 7.0, 12.5 Hz), 5.40 (d, 1H, J =7.1 Hz), 7.12-7.27 (m, 5H), 8.88 (br, 1H); ^{13}C NMR (75.4 mHz, $CDCl_3$) δ 37.5, 40.4, 42.7, 54.8, 127.2, 128.6, 129.3, 136.3, 157.2, 175.0, 207.6; HRMS (CI, isobutane) m/e 291.1358 (MH^+, calcd for $C_{15}H_{18}N_2O_4$: 291.1346).

C. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2(R)-hydroxy-3-methoxy-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

Th compound was pr pared in a manner according to th procedure described as G n ral Procedur A. The product of th prec ding Example (281 mg) was coupled with th product of Exampl 1C (300 mg) to yield crude product (427 mg) which was

chromatographed on silica eluted with ethyl acetate and a 1-4% ethanol in ethyl acetate gradient to yield the title compound (254 mg), (TLC R_f 0.5 in 18/2/1 $CHCl_3$-ethanol-NH_4OH).

LSIMS 579 (MH^+, 100%), 307 (70%).

Anal. Calcd for $C_{31}H_{38}N_4O_7 \bullet H_2O$: C, 62.40; H, 6.76; N, 9.39. Found: C, 62.28; H, 6.44; N, 9.23.

D. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (246 mg) was treated with periodinane. The product (215 mg, 87%), was isolated by extraction using ethyl acetate.

LSIMS 731 ($MH^+ + C_4H_{10}O_2S_2$, 8%), 577 (MH^+, 15%), 309 (100%).

Anal. Calcd for $C_{31}H_{36}N_4O_7 \bullet 1.25\ H_2O$: C, 62.14; H, 6.48; N, 9.35. Found: C, 62.05,; H, 6.09; N, 8.95.

Example 11

N^1-[4[4-(methylamino)piperidinyl]-1,4-dioxo-2(R)-(phenylmethyl)butyl]-N^a-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide hydrochloride

A. N^1-[4-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidinyl]-1,4-dioxo-2(R)-(phenylmethyl)butyl]-N^a-[2(R)-hydroxy-3-methoxy-3-oxo-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 1C (85 mg) and 4-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidinyl]-2(R)-(phenylmethyl)-1,4-butanedioic acid (100 mg) were coupled to give 160 mg of crude product which was purified on silica eluted with ethyl acetate-hexanes followed by ethyl acetate, to yield 110 mg (64%) of product, (TLC R_f 0.85 in 18/2/1 $HCCl_3$-ethanol-NH_4OH). LSIMS 693 (MH^+, 100%), 387 (90%).

B. N^1-[4-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidinyl]-1,4-dioxo-2(R)-(phenylmethyl)butyl]-N^a-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (90 mg) was treated

with the periodinane, and the crude product (78 mg) isolated by ethyl acetate extraction was purified on silica, eluted with ethyl acetate followed by 2% and 4% ethanol in ethyl acetate to yield the title product (45 mg, 50%), (TLC R_f 0.22 in ethyl acetate). LSIMS 691 (MH^+, 40%), 387 (100%).

C. N¹-[4-[4-(methylamino)piperidinyl]-1,4-dioxo-2(R)-(phenylmethyl)butyl]-N²-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide hydrochloride

The compound was prepared in a manner according to the procedure described as General Procedure B. The product of the preceding Example (37 mg) was treated with HCl-dioxane for 1 hour at 25°C to give 30 mg of the title substance.

LSIMS 623 ($MH^+ + CH_3OH$, 48%), 591 (MH^+), 287 (100%).

Example 12

N-[2,2-Difluoro-4-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-L-prolyl]amino]1,3-dioxo-5-phenylpent-1-yl] methylamine

A. N-[2,2-Difluoro-4-[N-[(1,1-dimethylethoxy)carbonyl]amino-3(R)-hydroxy-1-oxo-5-phenylpent-1-yl] methylamine

A large excess of anhydrous methylamine was introduced into a solution of ethyl 2,2-difluoro-4-[N-[(1,1-dimethylethoxy)carbonyl]amino]-3(R)-hydroxy-5-phenylpentanoate (J. Med. Chem. 1986, 29, 2080-2087, 200 mg) in ethanol (2 mL) at 0°C. After 2 hours at 25°C the mixture was concentrated and dried to yield 182 mg (94%) of a colorless solid, (TLC R_f 0.59 in ethyl acetate).

LSIMS 359 (MH^+, 60%), 303 (70%), 259 (100%).

B. N-[2,2-Difluoro-4-amino-3(R)-hydroxy-1-oxo-5-phenylpent-1-yl]methylamine hydrochloride

The product of the preceding example (173 mg) was converted by General Procedure B to the title substance (138 mg, 100%), (TLC R_f 0.5 in 18/2/1 CH_2Cl_2-ethanol-NH_4OH).

LSIMS 259 (MH^+, 100%).

C. N-[2,2-Difluoro-4-[[N-(1,1-dimethylethoxy)carbonyl]-L-prolyl]amino]-3(R)-hydroxy-1-oxo-5-phenylpent-1-yl] methylamine

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of the preceding Example (123 mg) and Boc-L-proline (86 mg) were coupled to yield 175 mg of crude product which was suspended

in dichloromethane and filtered. The filtered solid weighed 80 mg and was homogeneous by TLC (R_f 0.41 in 1:1 ethyl acetate-hexane).

LSIMS 456 (MH^+, 90%), 356 (100%).

D. N-[2,2-Difluoro-4-[[L-prolyl]amino]-3(R)-hydroxy-1-oxo-5-phenylpent-1-yl] methylamine hydrochloride

The compound was prepared in a manner according to the procedure described as Procedure B. The product of the preceding example (60 mg) was treated with HCl-dioxane to yield 66 mg of the title substance, (TLC R_f 0.46 in 18:2:1 CH_2Cl_2-ethanol-NH_4OH). ^1H NMR showed that the sample contained p-dioxane.

LSIMS 356 (MH^+, 100%).

E. N-[2,2-Difluoro-4-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-L-prolyl]amino]-3(R)-hydroxy-1-oxo-5-phenylpent-1-yl] methylamine

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of the preceding example (60 mg) was coupled to Boc-L-leucine (38 mg) and the crude product (84 mg) was purified on silica eluted with ethyl acetate-hexane to yield the title substance (49 mg, 58%), TLC (R_f 0.32 ethyl acetate).

LSIMS 569 (MH^+, 100%), 469 (85%), 356 (50%).

F. N-[2,2-Difluoro-4-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-L-prolyl]amino]-1,3-dioxo-5-phenylpent-1-yl] methylamine

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (46 mg) was treated with the periodinane, and the crude product (54 mg), isolated by ethyl acetate extraction, was purified on silica eluted with ethyl acetate-hexanes, to yield the title product (28 mg, 62%). LSIMS 585 ($MH^+ + H_2O$, 20%), 567 (MH^+, 60%), 467 (100%), 354 (30%).

Example 13

N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2-(2-benzothiazolyl)-2-oxo-1-(phenylmethyl)ethyl]-L-prolinamide

A. N-(morpholino-1-carbonyl)-L-phenylalanyl-L-proline benzyl ester

N-(morpholino-1-carbonyl)-L-phenylalanine (12.6 g) and L-proline benzyl ester hydrochloride (10.0 g) were coupled according to General Procedure A and the crude

product purified on silica gel eluted with ethyl acetate-hexanes followed by ethyl acetate to yield 10.0 g (53%) of the title product, (TLC R_f 0.26 in ethyl acetate).

LSIMS 466 (MH^+, 28%), 309 (50%), 119 (100%).

B. N-(morpholino-1-carbonyl)-L-phenylalanyl-L-proline

and

N-(morpholino-1-carbonyl)-L-phenylalanyl-L-proline dicyclohexylamine salt

A solution of the product of the preceding Example (9.9 g, 21.0 mmol) in methanol (90 mL) and acetic acid (10 mL) was shaken with 10% palladium-on-carbon (1.1 g) at 25°C under 45 p.s.i. hydrogen pressure for 30 minutes. The mixture was filtered through Supercel (trademark), the cake washed with 10:1 methanol-acetic acid, and the filtrate concentrated. The resulting oil was dissolved in chloroform (200 mL) and the resulting solution washed with water (3 x 40 mL), brine, dried ($MgSO_4$) and concentrated to yield 6.44 g (82%) of the free acid, (TLC R_f 0.52 in 18/2/1 $HCCl_3$-ethanol-acetic acid). A portion (0.5 g) of this material was dissolved in dichloromethane and 0.26 mL (1.0 equiv) dicyclohexylamine was added. The mixture was concentrated and the residue dissolved with heating in ethyl acetate (5 mL). Hexane (15 mL) was added while the mixture was kept at reflux. Cooling (0°C) produced a solid which was recrystallized in like fashion from ether (2 mL) and hexanes (20 mL) to yield 430 mg of a granular powder.

Anal. Calcd for $C_{19}H_{25}N_3O_5 \bullet C_{12}H_{23}N \bullet H_2O$: C, 64.78; H, 8.77; N, 9.75. Found: C, 64.86; H, 8.67; N, 9.71.

C. 1(R,S), 2(S)-1-(2-benzothiazolyl)-2-[N-[(1,1-dimethylethoxy)carbonyl]amino]-3-phenyl-1-propanol

N-Butyllithium in hexane (1.88 mL, 4.7 mmol) was added dropwise to a -78°C solution of benzothiazole (0.62 g, 4.6 mmol) in tetrahydrofuran (5 mL) and the resulting mixture was stirred at -78°C for 30 minutes. A solution of 2-[N-[(1,1-dimethylethoxy)carbonyl]amino]-3-phenyl-1-propanal was added and the mixture was stirred for 30 minutes at -78°C. The mixture was warmed at 0°C and treated with saturated aqueous NH_4Cl (6 mL). Ethyl acetate (100 mL) was added and the resulting solution was washed twice with water, brine, dried ($MgSO_4$) and concentrated to yield 1.17 g of crud product which was purified on silica eluted with thyl acetate-hexanes to yi ld th titl compound (220 mg, 12%).

LSIMS 385 (MH^+, 20%), 309 (100%).

D. 1(R,S), 2(S)-1-(2-benzothiazolyl)-2-amino-3-phenyl-1-propanol hydrochloride

The compound was prepared in a manner according to the procedure described as Procedure B. The product of the preceding Example (215 mg) was converted to the title hydrochlorides (189 mg), (TLC R_f 0.75 and 0.72), 18/2/1 CH_2Cl_2-ethanol-NH_4OH).

EI-MS 284 (M^+).

E. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2-(2-benzothiazolyl)-1(R,S)-hydroxy-1-(S)-phenylmethyl)ethyl]-L-prolinamide

The product of Example 13B (DCHA salt) (395 mg) was coupled to the product of the preceding Example (189 mg) using General Procedure A, to yield 285 mg of crude product which was purified on silica eluting with a gradient (0.5-4%) of ethanol in dichloromethane. Yield, 191 mg, 50%, (TLC R_f 0.74, 9:1 dichloromethane-ethanol). RP-HPLC (50/50 System A) showed a 1.2:1 mixture of isomers.

LSIMS 642 (MH^+, 30%), 309 (100%).

F. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2-(2-benzothiazolyl)-2-oxo-1-(phenylmethyl)ethyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (191 mg) was treated with the periodinane, and the crude product (100 mg), isolated by ethyl acetate extraction, was purified on silica eluted with ethyl acetate to yield the title product (30 mg, 16%), (TLC R_f 0.56 in 18/2/1 CH_2Cl_2-ethanol-NH_4OH).

LSIMS 640 (MH^+, 90%), 380 (40%), 309 (40%).

Example 14

N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

A. N-[3,3,3-Trifluoro-2-hydroxy-1-(phenylmethyl)propyl]benzamide

Sodium borohydride (1.43 g, 37.7 mmol) was added to a solution of N-[3,3,3-trifluoro-2-oxo-1-(phenylmethyl)propyl]benzamide (racemate, J. Med. Chem. 1990, 33, 394-407, compound 4c therein) in absolute ethanol (100 mL) at 25°C. After 4 hours the mixture was poured into a mixture of ice, excess 6N HCl, and chloroform, and the resulting mixtur extract d r peatedly with chloroform until no more solid remained. Th combin d organic layers w r dried and concentrated to yield the titl compound (9.51 g, 78%).

LSIMS 324 (MH^+, 100%).

B. 3-Amino-4-phenyl-1,1,1-trifluoro-2-butanol Hydrochloride

The product of the preceding Example (9.5 g, 29.6 mmol) was dissolved in a mixture of 12N HCl (400 mL), H_2O (200 mL) and ethanol (200 mL) and the resulting solution was heated at reflux for 24 hours. The mixture was concentrated and the residue, a colorless solid, was dissolved in H_2O. The resulting solution was extracted with ether (5 x 100 mL) and the aqueous layer concentrated in vacuo. The resulting light yellow solid was recrystallized from ethyl acetate-hexanes to yield the title substance (3.9 g, 52%), (TLC R_f 0.70 in 18/2/1 CH_2Cl_2-ethanol-NH_4OH). Further material precipitated and was filtered from the mother liquors (3.1 g).

C. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2(R,S)-hydroxy-3,3,3-trifluoro-1(S)-(phenylmethyl)propyl]-L-prolinamide

and

N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2(R,S)-hydroxy-3,3,3-trifluoro-1(R)-(phenylmethyl)propyl]-L-prolinamide

The product of Example 13B (free acid, 404 mg) and the product of the preceding Example (250 mg) were coupled according to General Procedure A, to yield 500 mg of crude product which was purified on silica eluting with ethyl acetate-hexanes. Three fractions were thus obtained (distinguished by TLC): less polar material (135 mg, 24%, TLC R_f 0.21 in ethyl acetate), more polar material (164 mg, 29%, TLC R_f 0.16 in ethyl acetate), and a mixture (119 mg, 21%) of the above. Less polar band: LSIMS 577 (100%, MH^+), 317 (50%), 261 (50%), 233 (40%). More polar band 577 (MH^+, 100%), 317 (80%), 261 (80%), 233 (65%).

D. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The less polar product of the preceding Example ((125 mg) was converted by Procedure C (ethyl acetate extraction) to 117 mg of crude material which was purified on silica gel eluted with ethyl acetate-hexanes followed by ethyl acetate to yield 72 mg (57%) of the title substance, (TLC R_f 0.40 in ethyl acetate). By HPLC (50/50 System B), less than 0.5% of the isomeric product of Example 15 was present in this sample. No isomerization f the title substanc to the product of Example 15 occurred in 24 hours at 25°C in 1:1 acetonitrile-pH 7 phosphate buffer (HPLC, System B). In contrast, a

sample stored in 1:1 acetonitrile-pH 9 borate buffer for 18 hours isomerized to a 1.2: 1 mixture of the title substance and that of Example 15, respectively.

LSIMS 593 ($MH^+ + H_2O$, 50%), 575 (MH^+, 40%), 261 (90%), 233 (100%).

Example 15

N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(R)-(phenylmethyl)propyl]-L-prolinamide

The more polar product of the preceding Example (155 mg) was converted by Procedure C (ethyl acetate extraction) to 119 mg of crude material which was purified on silica gel eluted with ethyl acetate-hexanes followed by ethyl acetate to yield 55 mg (35%) of the title substance, (TLC R_f 0.20 in ethyl acetate). By HPLC (50/50 System B), about 5% of the product of Example 14D was present in this sample (retention times 4.96 (product of the instant Example) and 5.46 minutes (product of Example 14d). This material stored in 1:1 acetonitrile-pH 9 borate buffer for 18 hours isomerized to a 1:1.2 mixture of the title substance and that of Example 14D, respectively.

LSIMS 593 ($MH^+ + H_2O$, 60%), 575 (MH^+, 20%), 333 (40%), 261 (70%), 233 (40%).

Example 16

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

A. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-L-proline benzyl ester

The product of Example 10B (30.5 g) was coupled to proline benzyl ester using General Procedure A and the crude product (45.3 g) triturated three times with hexanes to yield 43.4 g of an orange solid. A portion (38.1 g) of this material was dissolved with heating in 260 mL ethyl acetate and 100 mL hexanes was added. The resulting solution on standing 15 hours at 25°C deposited light beige crystals which were collected by filtration and washed with hexanes to yield 5.44 g of the title substance, (TLC R_f 0.16 in ethyl acetate). Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.35; H, 6.37; N, 8.67.

B. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-L-proline

The product of the preceding Example (3.0 g, 6.28 mmol) was shaken with 300 mg of 20% $Pd(OH)_2/C$ in 30 mL methanol and 3 mL acetic acid for 1 hour at 25°C and 50 p.s.i. hydr g n pressure. The r sulting mixtur was filtered through Supercel (trademark) and th cak wash d well with methanol. The filtrat was concentrated and

the residue dissolved in ethyl acetate (50 mL). The resulting solution was washed with water (3 x 25 mL) and brine (25 mL). Tetrahydrofuran (25 mL) and 1N HCl (25 mL) were added, and the resulting mixture stirred at 25°C for 15 minutes. The aqueous layer was separated and the organic layer dried and concentrated. The dried residue weighed 510 mg (21%) and was homogeneous by TLC (R_f 0.3 in 18/2/1 $CHCl_3$-ethanol-acetic acid).

LSIMS 388 (MH^+, 85%), 273 (100%), 245 (55%). The aqueous layers were saturated with NaCl and extracted twice with chloroform to yield an additional 1.80 g (74%) of product.

C. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2(R,S)-hydroxy-3,3,3-trifluoro-1(S)-(phenylmethyl)propyl]-L-prolinamide

and

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2(R,S)-hydroxy-3,3,3-trifluoro-1(R)-(phenylmethyl)propyl]-L-prolinamide

The product of the preceding Example (500 mg) and the product of Example 14B (300 mg) were coupled according to General Procedure A, to yield 659 mg of crude product which was purified on silica eluting with ethyl acetate-hexanes, ethyl acetate, and 1% ethanol in ethyl acetate. Three fractions were thus obtained (distinguished by TLC): less polar material (184 mg, 27%; TLC R_f 0.58 in 18/2/1 CH_2Cl_2-ethanol-NH_4OH), more polar material (228 mg, 33%; TLC R_f 0.44 in 18/2/1 CH_2Cl_2-ethanol-NH_4OH), and a mixture (121 mg, 17%) of the above.

D. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The less polar product of the preceding example (163 mg) was oxidized according to General Procedure C, and the crude product (116 mg), isolated by chloroform extraction, was purified on silica eluted with ethyl acetate-hexanes, ethyl acetate, and 1% ethanol in ethyl acetate to yield the title substance (98 mg, 84%), (TLC R_f 0.16 in ethyl acetate). By RP-HPLC (40/60 System B) this product contained 3% of the less-retained product of Example 17.

LSIMS 605 (20%, $MH^+ + H_2O$), 587 (40%, MH^+), 333 (80%), 315 (70%), 273 (70%), 245 (100%).

Anal. Calcd for $C_{30}H_{33}N_4O_5F_3 \cdot 1.5\ H_2O$: C, 58.71; H, 5.91; N, 9.13. Found: C, 59.04; H, 5.82; N, 8.96.

Example 17

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(R)-(phenylmethyl)propyl]-L-prolinamide

The more polar product of Example 16D was (153 mg) was oxidized according to General Procedure C, and the crude product (90 mg), isolated by chloroform extraction, was purified on silica eluted with ethyl acetate-hexanes, ethyl acetate, and 1% ethanol in ethyl acetate to yield the title substance (35 mg, 23%). RP-HPLC indicated this product contained 7% of the more retained product of Example 16D.

LSIMS 633 ($MH^+ + C_2H_5OH$, 40%), 605 (30%, $MH^+ + H_2O$), 587 (MH^+, 40%), 361 (60%), 333 (40%), 315 (60%), 273 (70%), 245 (70%).

Example 18

N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(cyclohexylmethyl)propyl]-L-prolinamide

A. 2-Nitro-1-cyclohexylethane

2-cyclohexylethyl bromide (50 g, 0.26 mol) was added to a mixture of sodium nitrite (31 g, 0.45 mol) in dimethylformamide (500 mL) at 5°C and the mixture was stirred for 10 hours at 5°C and for 8 hours at 20°C. The resulting solution was poured into ice-water (1.5 L) and the mixture extracted with petroleum ether (3 times 150 mL). The organic layers were combined and washed with water, dried, and concentrated. The residue was distilled through an 8 inch fractionating column to yield a lower-boiling material and 18.3 g of colorless liquid, bp 70-80°C at 2 Torr. The latter was redistilled in the same apparatus with further separation of a low boiling fraction to yield 16.4 g of colorless liquid, bp 45-55°C at 0.5 Torr, containing less than 2% of the lower boiling impurity which was identified as the corresponding nitrite ester. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.57; H, 9.47; N, 9.37.

B. 3-Nitro-4-cyclohexyl-1,1,1-trifluoro-2-butanol

CAUTION! A caution has been raised that the distillation of substances of this type can lead to explosion (USP 5055450).

A mixture of the product of the previous Example (15.2 g, 96.7 mmol) and anhydrous potassium carbonate (200 mg, 1.45 mmol) was treated at 25°C with trifluoroac taldehyde hydrat (16.8 g, 145 mmol and the mixture was stirred at 50°C for 4 h urs and at 60°C for 8 hours. The mixtur was chromatographed on 100 g silica lut d with 1:10 ether-hexanes to yield 24 g of impure product which was

chromatographed on 300 g silica eluted with 1:15 and 1:10 ether-hexanes to yield 20.2 g (82%) of the title product as a light yellow oil, (TLC R_f 0.50 and 0.42 in 1:2 ether-hexanes).

C. 3-Amino-4-cyclohexyl-1,1,1-trifluoro-2-butanol

A solution of the product of the preceding Example (20.1g, 0.078 mol) in ethanol was shaken with water-wet Raney nickel (5 g) (Aldrich Chemical Co.) under 45 p.s.i. hydrogen pressure at 25°C for 16 hours. The mixture was filtered through Supercel, and the cake washed well with methanol. The filtrates were concentrated to yield a greenish waxy solid which was washed on the filter with hexanes and dried; 11.02 g (62%) of the title substance was thus obtained as a colorless solid, (TLC R_f 0.1 (major substance) and 0.3 (minor substance) in ethyl acetate).

D. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[2-hydroxy-3,3,3-trifluoro-1-(cyclohexylmethyl)propyl]-L-prolinamide

The product of Example 13B (363 mg) was coupled to the product of the preceding Example (239 mg) by General Procedure A, and the crude product (514 mg) was purified on silica and sequentially eluted with ethyl acetate-hexanes, ethyl acetate, 1% and 2% ethanol in ethyl acetate to yield 446 mg (79%) of the title substance as a mixture of (presumably four) isomers, (TLC R_f 0.61 and 0.59 in 18/2/1 CH_2Cl_2-ethanol-NH_4OH).

LSIMS 583 (MH^+, 60%), 323 (50%), 307 (100%).

E. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(cyclohexylmethyl)propyl]-L-prolinamide

The product of the preceding Example (419 mg) was oxidized by General Procedure C to give 372 mg of crude product, isolated by dichloromethane extraction, which was purified on silica and sequentially eluted with 1%, 2% and 4% ethanol in 1:1 ethyl acetate-dichloromethane. Two fractions were obtained, the less polar title substance (39 mg 9%; TLC R_f 0.21 in 1:1:0.1 ethyl acetate-CH_2Cl_2-ethanol), and the product of the following Example.

LSIMS 613 ($MH^+ + CH_3OH$, 10%), 599 ($MH^+ + H_2O$, 10%), 581 (MH^+, 40%), 261 (100%), 233 (60%).

F. N-(morpholino-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(R,S)-(cyclohexylmethyl)propyl]-L-prolinamide

The second product to elute from the chromatography of the product of the preceding example was a mixture of the above substance and the more polar 1(R) isomer (294 mg, 70%; TLC R_f 0.15 in 1:1:0.1 ethyl acetate-CH_2Cl_2-ethanol). The two substances contained in this product were not distinguishable by RP-HPLC in System B (60/40).

LSIMS 627 ($MH^+ + C_2H_5OH$, 599 ($MH^+ + H_2O$), 581 (MH^+ 33%), 261 (100%), 233 (60%).

Anal. Calcd for $C_{29}H_{39}N_4O_5F_3 \cdot 2.3\ H_2O$: C, 55.99; H, 7.06; N, 9.01. Found: C, 56.17; H, 6.67; N, 8.54.

Example 19

N-(4-(methylamino)piperidine-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

A. N-(4-(methylamino)piperidine-1-carbonyl)-L-phenylalanyl-L-proline benzyl ester

Sodium cyanoborohydride (441 mg, 1.2 equiv) was added to a mixture of the product of Example 16A (2.79 g, 5.84 mmol), methylamine hydrochloride (1.972 g, 29.2 mmol), anhydrous sodium acetate (4.79 g, 58.4 mmol), and 3Å molecular seives (600 mesh, 2.8 g) in methanol (30 mL) at 0°C and the mixture was stirred at 25°C for 16 hours. The mixture was filtered through Supercel (trademark) and the filtrate concentrated. The residue was dissolved in ethyl acetate (125 mL) and the resulting solution washed with 1N NaOH (3 times 20 mL), dried and concentrated. The residue was chromatographed on 100 g silica packed in 1% ethanol/1% NH_4OH-dichloromethane and eluted with this solvent, followed by 2%, 5%, 10%, 20%, and 40% ethanol-dichloromethane (500 mL portions, all containing 1% NH_4OH), to yield the title substance (2.45 g, 85%), (TLC R_f 0.35 in 1:4 ethanol-dichloromethane containing 1% NH_4OH).

LSIMS 493 (MH^+, 100%), 288 (80%).

B. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-phenylalanyl-L-proline benzyl ester

Di-t-butyldicarbonat (1.17 mL, 5.1 mmol) was add d to a solution of the product of the pr c ding Example (2.29 g, 4.64 mmol) in t trahydrofuran (15 mL) at

25°C and the resulting mixture was stirred at 25°C for 15 hours. The mixture was concentrated, the residue dissolved in ethyl acetate (100 mL) and the resulting solution was sequentially washed with 1N HCl (20 mL), brine, dried, and concentrated to yield 2.8 g of the title product, (TLC R_f 0.3 in ethyl acetate).

LSIMS 593 (MH^+, 70%), 388 (100%).

C. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-phenylalanyl-L-proline

A solution of the product of the preceding Example (2.50 g, 4.23 mmol) in methanol (40 mL) was shaken with 300 mg 20% $Pd(OH)_2/C$ at 50 p.s.i. hydrogen pressure at 25°C for 15 hours. The mixture was filtered through Supercel (trademark) and the filtrate concentrated and dried to yield 2.36 g of the title substance, (TLC R_f 0.59 in 18/2/1 $CHCl_3$-ethanol-HOAc).

LSIMS 503 (MH^+, 50%), 388 (100%).

D. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-phenylalanyl-N-[2(R,S)-hydroxy-3,3,3-trifluoro-1(S)-(cyclohexylmethyl)propyl]-L-prolinamide

and

N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-phenylalanyl-N-[2(R,S)-hydroxy-3,3,3-trifluoro-1(R)-(cyclohexylmethyl)propyl]-L-prolinamide

The product of the preceding Example (649 mg) was coupled to the product of Example 14B (300 mg) by General Procedure A and the crude product (765 mg) was purified on silica and sequentially eluted with 2.5%, 5%, 10% and 20% ethanol in 1:1 dichloromethane-ethyl acetate to yield the less polar, first-titled product (78 mg, 9%), (TLC R_f 0.19 in 0.1:1:1 ethanol-dichloromethane-ethyl acetate).

LSIMS 704 (35%, MH^+), 388 (100%).

Also obtained was the more polar, second-titled product (194 mg, 23%), (TLC R_f 0.09 in the same TLC system), LSIMS 704 (35%), 388 (100%). A third fraction containing 208 mg (25%) of a mixture of the two products was also obtained.

E. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The first-titled, less polar product of the preceding Example (65 mg) was oxidized by General Procedure C to yield crude product (67%), which was isolated by chloroform extraction. The crude product was purified on silica and eluted with ethyl acetate-dichloromethane to yield 52 mg of the title substance, (TLC R_f 0.24 in 0.1:1:1 ethanol-dichloromethane-ethyl acetate).

LSIMS 748 ($MH^+ + C_2H_5OH$, 5%), 720 ($MH^+ + H_2O$, 10%), 702 (MH^+, 18%), 388 (100%).

The title product was also obtained alternatively by oxidation of the third fraction referred to in Example 19D (mixture of first and second-titled products of Example 19D) (188 mg) according to General Procedure C, to yield crude product (191 mg) which was isolated by chloroform extraction and purified on silica, and sequentially eluted with 1%, 2% and 4% ethanol in 1:1 dichloromethane-ethyl acetate. The less polar substance (91 mg) was identical by TLC and NMR to that obtained immediately above and different from the product of Example 20A. A mixture of this substance and a more polar product was also obtained (99 mg).

F. N-(methylamino)piperidine-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride

The product of the preceding Example (78 mg) was dissolved in trifluoroacetic acid (1 mL) at 25°C for 30 minutes. The mixture was concentrated, the residue dissolved in ethanol (1 mL) and the resulting solution treated with 0.20 mL 1N HCl. The solution was concentrated and the crude product ground to a fine powder, triturated with ether and dried (61 mg, 87%). The product of Example 20B could not be detected in this material by RP-HPLC (30/70), System B.

LSIMS 634 ($MH^+ + CH_3OH$), 602 (MH^+, 309 (33%). A sample which was heated at 55°C for 18 hours showed about 20% conversion to the product of Example 20B.

Example 20

N-(4-(methylamino)piperidine-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(R)-(phenylmethyl)propyl]-L-prolinamide

A. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(R)-(phenylmethyl)propyl]-L-prolinamide

The second-titled, more polar product of Example 19E (174 mg) was oxidized by General Procedure C to yield crude product (168 mg), isolated by chloroform extraction, which was purified on silica eluted with 1%, 2%, and 4% ethanol-dichloromethane to yield the title substance (124 mg, 71%), (TLC R_f 0.11 in 0.1:1:1 ethanol-dichloromethane-ethyl acetate).

LSIMS 748 ($MH^+ + C_2H_5OH$, 10%), 702 (MH^+, 20%), 388 (100%).

B. N-(4-(methylamino)piperidine-1-carbonyl)-L-phenylalanyl-N-[3,3,3-trifluoro-2-oxo-1(R)-(phenylmethyl)propyl]-L-prolinamide

The product of the preceding Example (54 mg) was treated sequentially with trifluoroacetic acid and 1N HCl as described for the preparation of the product of Example 19F. The crude product was redissolved in ethanol, filtered, concentrated, and the residue triturated with ether and dried at 25°C to yield 35 mg (72%) of a colorless powder. The product of Example 19F was distinguishable from and not present in this product by RP-HPLC.

LSIMS 648 ($MH^+ + C_2H_5OH$, 5%), 634 ($MH^+ + CH_3OH$, 20%), 620 ($MH^+ + H_2O$, 10%), 602 (MH^+, 15%), 288 (100%). Anal. Calcd for $C_{31}H_{39}N_5O_4ClF_3 \cdot 3H_2O$: C, 53.79; H, 6.55; N, 10.12. Found: C, 53.82; H, 6.25; N, 9.97.

Example 21

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride

A. N-(4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino)piperidine-1-carbonyl) -L-valine benzyl ester

A solution of L-valine benzyl ester p-toluenesulfonate (7.13 g, 18.8 mmol) and triethylamine (2.90 mL, 20.6 mmol) in dichloromethane (40 mL) was added to a stirred 0-5°C slurry of carbonyldiimidazole (3.34 g, 20.6 mmol) and imidazole (2.56 g, 37.6 mmol) in dichloromethan (95 mL) and the resulting mixtur was stirred at 25°C for 30 min. A solution of 4-[N-[(1,1- dimethyl thoxy)carbonyl]methylamino)piperidine (EP

457,686, Example 11B therein, 4.00 g, 18.8 mmol) in dichloromethane (20 mL) was added and the mixture stirred at 25°C for 7 days. The resulting solution was washed with 2N HCl (2 x 100 mL), 1N NaOH, dried, and concentrated. The residue was chromatographed on silica eluted with ethyl acetate-hexanes giving the title substance (5.54 g, 66%). ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J= 6.9 Hz), 0.91 (d, 3H, J = 6.9 Hz), 1.44 and 1.45 (s, 1:9 ratio, 9H total), 1.5-1.7 (m, ca. 4H), 2.14 (m, 1H), 2.68 and 2.71 (s, ca. 9:1 ratio, 3H total), 2.85 (m, 2H), 4.04 (br and m, 3H total), 4.48 (dd, 1H, J = 4.7, 8.4 Hz), 4.94 (d, 1H, J = 8.3 Hz), 5.10 (d, A of AB, 1H, J = 12.2 Hz), 5.20 (d, B of AB, 1H, J = 12.2 Hz), 7.34 (m, 5H). Anal. Calcd for $C_{24}H_{37}N_3O_5 \bullet 0.25\ H_2O$: C, 63.76; H, 8.36; N, 9.29. Found: C, 63.98; H, 8.11; N, 9.07.

B. N-(4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino)piperidine-1-carbonyl) -L-valine

The product of the preceding example (5.14 g, 11.5 mmol) was added to 1.5 g of Pd(OH)2/C (20% Pd content, Aldrich) in methanol (65 mL) and the resulting mixture was shaken under 30 p.s.i. hydrogen pressure for 30 min. The mixture was filtered through methanol-washed filter aid and the filtrates were concentrated giving the title product as a colorless foam (3.96 g, 97%). ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.8 Hz), 1.45 (s, 9H), 1.5-1.75 (m, 4H), 2.19 (m, 1H), 2.69 (s, 3H, NCH_3), 2.85 (m, 2H, $CONCH_2$), 4.2- 4.0 and 4.04 (br and m, 3H total, CONCH and $CONCH_2$), 4.25 (dd, 1H, NCHCO), 5.07 (d, 1H, J = 8.1 Hz, NH). Anal. Calcd for $C_{17}H_{31}N_3O_5$: C, 57.12; H, 8.74; N, 11.76. Found, C, 55.56; H, 8.17; N, 10.92.

C. N-(4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino)piperidine-1-carbonyl) -L-valyl-L-proline benzyl ester

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of the preceding Example (2.26 g, 6.32 mmol) was coupled to proline benzyl ester hydrochloride (1.53 g, 6.33 mmol) to yield crude product (2.96 g, 86%) which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, J = 6.7 Hz), 0.98 (d, 3H, J = 6.7 Hz), 1.44 (s, 9H), 1.5-1.7 (m, ca. 4H), 1.9-2.1 (m, ca. 4H), 2.20 (m, 1H), 2.68 (s, 3H), 2.80 (m, 2H), 3.65 (m, 1H), 3.88 (m, 1H), 4.0-4.2 (m, 3H), 4.45 (dd, 1H, J = 6.7, 8.7 Hz), 4.54 (dd, 1H, J = 5.2, 8.8 Hz), 5.12 (d, A of AB, 1H, J = 12.3 Hz), 5.17 (d, B of AB, 1H, J = 12.3 Hz), 7.32 (m, 5H). Anal. Calcd for $C_{28}H_{44}N_4O_6 \bullet 0.5H_2O$: C, 62.90; H, 8.19; N, 10.11. Found: C, 62.88; H, 8.16; N, 9.99.

D. N-(4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino)piperidine-1-carbonyl) -L-valyl-L-proline

According to the procedure for the preparation of the compound of Example 21b the product of the preceding Example (2.83 g, 5.35 mmol) gave 2.31 g (95 %) of the title substance as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, J = 6.6 Hz), 0.98 (d, 3H, J = 6.6 Hz), 1.44 (s, 9H), 1.5-1.7 (m, 4H), 2.05 (m, 3H), 2.20 (m, 2H), 2.68 (s, 3H), 2.80 (m, 2H), 3.62 (m, 1H), 3.92 (m, 1H), 4.05 in 4.0-4.2 (m over br, 3H total), 4.41 (m, 1H), 4.53 (m, 1H), 4.9-5.3 (br, 1H), 5.50 (d, 1H, J = 8.6 Hz). LSIMS 455 (MH^+, 30%), 340 (100%), 284 (30%), 256 (20%), 185 (38%). Anal. Calcd for $C_{22}H_{38}N_4O_6 \bullet H_2O$: C, 55.91; H, 8.53; N, 11.86. Found: C, 55.74; H, 8.46; N, 11.57.

E. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl] -L-valyl-N-[2(R,S)-hydroxy-3,3,3-trifluoro-1(R,S)-(cyclohexylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of the preceding Example (463 mg, 1.02 mmol) was coupled to the product of Example 14B to give 673 mg (103%) of the title substance as a mixture of diastereomers which was used without further purification. ^{1}H NMR ($CDCl_3$, partial) δ 0.9-1.0 (doublets, 6H, $(CH_3)_2CH$), 1.45 (s, 9H, $(CH_3)_3C$), 2.7 and 2.72 (singlets, 1:1 ratio, 3H total, NCH_3), 7.1-7.4 (m, 5H, aromatic). ^{19}F NMR showed four doublets (J = ca. 7 Hz) in 3:1:2:5 ratio at -74.54, -75.02, -75.18, and -75.5 ppm, respectively. Four additional doublets were observed (8% of the total integration) between -76.4 and -77.5 ppm. LSIMS 656 (MH^+, 20%), 340 (100%), 317 (20%), 284 (20%), 256 (18%), 185 (35%).

F. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl] -L-valyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The product of the preceding Example (560 mg, 0.87 mmol) was oxidized by General Procedure C to give 514 mg of crude product, isolated by chloroform extraction, which was purified on silica eluted with 1:1 dichloromethane-ethyl acetate, followed by 1%, 2%, 4%, and 10 % ethanol in 1:1 dichloromethane- ethyl acetate. Three fractions were obtained, the less polar title product (151 mg), the more polar product of the following example, and a mixture of the two substances (127 mg). The less polar titl product contained less than 1% of the more polar product of the following example by HPLC. ^{1}H NMR ($CDCl_3$, 300 mHz) δ 0.79 (d, 0.4H, J = 6.8 Hz), 0.83 (d, 0.4H, J = 6.8 Hz), 0.94 (d, 2.6H, J = 6.7 Hz), 0.99 (d, 2.6H, J = 6.6 Hz), 1.46

(s, 9H), 1.55-2.0 (m, ca. 7H), 2.16 (m, 1H), 2.68, 2.69, and 2.72 (s, ca. 2:2.5:9 ratio, ca. 3H total), 2.75-3.1 (m, ca. 3H), 3.35 (dd, 1H), 3.88 (m, 1H), 3.95-4.15 (m, ca.3H), 4.37 (d, 1H, J = 7.6 Hz), 4.55 (dd, ca. 0.2H), 4.64 (m, 1H), 4.89 (d, 1H, J = 7.8 Hz), 5.04 (m, ca 0.5H), 7.1-7.35 (m, 5H), 7.4 (d, 1H). ^{19}F NMR (282.4 mHz, $CDCl_3$) δ -76.0, -76.5; -82.4, -82.5 (0.5: 2:5.7:1.3 intensity ratio, respectively). The ratio of the combined integrals of the -82.4 and -82.5 resonances (presumably hydrate) to the -76.5 and -76.0 resonances (presumably ketone) was 6.33. It is presumed that nonequivalent rotational isomers were observed. LSIMS 700 ($MH^+ + C_2H_5OH$, 8%), 672 ($MH^+ + H_2O$, 8%), 654 (MH_+, 10%), 340 (100%), 284(20%), 256 (18%), 185 (38%). Anal. Calcd for $C_{32}H_{46}N_5O_6F_3 \bullet 1.25\ H_2O$: C, 56.83; H, 7.23; N, 10.36. Found: C, 56.68; H, 7.16; N, 10.14.

G. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-valyl-N-[3,3,3-trifluoro-2-oxo-1(R)-(phenylmethyl)propyl]-L-prolinamide

A second substance eluted from the chromatography of the product of the preceding example (103 mg). HPLC showed it to contain about 10% of the product of the preceding example. ^1H NMR ($CDCl_3$, 300 mHz) δ 0.8-1.0 (overlapping d, 6H total), 1.45 and 1.46 (s, 9H total), 1.5-2.0 (m, ca 7 H), 2.3 (m, ca. 0.5H), 2.68 and 2.69 (s, 3H total), 2.75- 2.9 (m, ca. 2H), 3.11 (m, ca. 0.5H), 3.21 (dt, 1H), 3.38 (m, ca. 0.5H), 3.5 (m, 1H), 3.77-4.25 (m, ca. 4.5H), 4.25-4.5 (m, 1.5H), 4.55 (d, 0.5H), 5.0-5.2 (m, 1H), 6.05 (d, 0.2H), 6.75 (d, 0.3H), 7.1-7.35 (m, 5H), 7.75 (d, 0.2H). ^{19}F NMR ($CDCl_3$, 282.4 mHz) δ -75.9 (s, 0.45 F), -76.1 (s, 0.12 F), -76.5 (0.03 F), -76.6 (s, 0.72 F), -77.0 (s, 0.12F), -81.5 (s, 0.03F), -81.7 (s, 0.87 F), -82.3 (s, 0.21F), -82.7 (s, 0.45 F). The -76.5 and -82.3 resonances (0.25 F, ca. 10% of total) are attributed to the 1(S) diastereomer (product of Example 21f) which was present by HPLC at approximately the 10% level. LSIMS 700 (MH^{+}+C2H5OH, 10%), 654 (MH^+, 10%), 340 (100%), 284 (20%), 256 (20%), 185 (36%). Anal. Calcd for $C_{32}H_{46}N_5O_6F_3 \bullet 1.25\ H_2O$: C, 56.83; H, 7.23; N, 10.36. Found: C, 56.81; H, 7.18; N, 10.20.

H. N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride

The product of Example 21f (122 mg, 0.186 mmol) was dissolved at 0°C in trifluoroacetic acid (4 mL) and th resulting solution was stirred at this temperature for 15 min. The mixture was evaporated and th residu dried at 0.05 mm and dissolved in s veral mL isopropyl alcohol. The r sulting solution was treated with 1N HCl (0.2

mL) and concentrated. The residue was dried at 0.05 Torr for 30 min and the residual oil triturated to a colorless solid with ether. Drying gave the title substance (105 mg, 96%) as a colorless solid. HPLC (retention time 5.93 min, 30/70 System B) showed none of the isomeric substance of Example ^{1}H NMR (D_2O, 300 mHz) δ 0.84 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.8 Hz), 1.44 (m, 2H), 1.64 (m, 1H), 1.7-1.95 (m, 3H), 2.00 (m, 1H), 2.08 (m, 2H), 2.66 (s, 3H), 2.73 (dd, 1H, J = ca. 9, 11 Hz), 2.88 (dt, 2H), 3.25 (m, 2H), 3.56 (m, 1H), 3.75 (m, 1H), 4.05 (m, 2H), 4.14 (d, 1H, J = 8.2 Hz), 4.30 (dd, 1H, J = 4.8, 8.5 Hz), 4.38 (dd, 1H, J = ca. 3, 8.4 Hz), 7.1-7.25 (m, 5H). Resonances attributable to the ketone form (present at 10% by ^{19}F NMR) were not distinguished in this or another sample where 33% of the ketone was present. ^{19}F NMR (D_2O, 282.4 mHz) δ -76.1 (s, 0.3 F), -82.3 (s, 2.7F). This spectrum was taken on the identical sample used to obtain the ^{1}H spectrum above. In a separate sample, the ratio of these resonances was 1:3, respectively. Two additional singlets at -82.5 comprising 13% of the total integration were also observed in the latter sample, and in equal or lesser amount in the former sample. LSIMS 554 (100, M^++H), 440 (45), 315 (50), 240 (50). Anal. Calcd for $C_{27}H_{38}N_5O_4F_3 \bullet HCl \bullet 3.5\ H_2O$: C, 49.65; H, 7.10; N, 10.72. Found: C, 49.96; H, 6.57; N, 10.44.

Example 22

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[3,3,3-trifluoro-2-oxo-1(R)-(phenylmethyl)propyl]-L-prolinamide hydrochloride

By the procedure of the preceding example (21h), the product of Example 21g (99 mg, 0.137 mmol) was deprotected with trifluoroacetic acid and converted to the title hydrochloride, which was triturated with ether, and thus obtained as a colorless solid (70 mg, 86%). HPLC (retention time 6.77 min, 30/70 system B) showed 10% of the isomeric product of Example 21h (5.9 min retention time). ^{1}H NMR (D_2O, 300 mHz) δ 0.8-1.1 (overlapping d, 6H total), 1.5 (m, 2H), 1.61 (m, 1H), 1.75 (m, 1H), 1.93 (m, ca. 3H), 2.12 (m, ca. 2H), 2.73 (s, 3H) overlapping 2.7 (m, 1H), 2.92 (m, 2H), 3.30 (m, ca 2H), 3.46 (m,1H), 3.78 (m, 1H), 4.06 (m, 2H), 4.18 (d, 1H, J = 8.4 Hz), 4.22 (t, 1H, J = ca. 8 Hz), 4.53 (dd, 1H), 7.2-7.4 (m, 5H). ^{19}F NMR (D_2O, 282.4 mHz) δ -76.1 (s, 0.75F), -82.1 (s, 2.25F). An additional resonance was observed at -82.3, comprising 10% of th total integration, which is attributed to the hydrate resonance of the L isomer, product of Example 21h, known to b a contaminant in this sample at the 10% level by HPLC. LSIMS 554 (70, M^++H), 440 (45), 300 (100), 240 (70). Anal. Calcd for

$C_{27}H_{38}N_5O_4F_3 \bullet HCl \bullet 3.5\ H_2O$: C, 49.65; H, 7.10; N, 10.72. Found: C, 49.58; H, 6.77; N, 10.43.

Example 23

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[2,3-dioxo-3-1-methylethoxy-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride

A. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-valyl-N-[2(R)-hydroxy-3-1-methylethoxy-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 21d (766 mg, 1.68 mmol) was coupled to isopropyl 3(S), 2(R)-3-amino-2-hydroxy-4- phenylbutanoate (USP 4,814,342, 400 mg, 1.68 mmol) to give 1.08 g (97%) of crude product which was purified on silica gel eluted with 50%, 67%, 75%, and 100% ethyl acetate in hexanes giving the title substance (669 mg, 60%). ^1H NMR ($CDCl_3$, partial) showed two rotamers in approximately 1:1 ratio, δ 0.94-1.01 (3-4 d, 6H total, J = ca. 7 Hz , valyl CH_3's), 1.18-1.27 (3-4 d, 6H total, J = ca. 7 Hz, $OCH(CH_3)_2$), 1.45 (s, 9H, Boc), 2.69 (2 s, 3H total, NCH_3), 4.91 and 4.99 (septets, 1H total, J = ca. 7 Hz, $OCH(CH_3)_2$), 5.14 (d, 1H, J = ca. 9Hz, partially exchanges in 8h with added D_2O), 6.98 (d, 1H, J = 9.6 Hz, little exchange in 8h with added D_2O), 7.44 (d, 1H, J = ca. 10 Hz, little exchange in 8h with added D_2O), 7.2-7.4 (m, 5H). LSIMS 674 (MH^+, 30%), 340 (85%), 335 (100%), 284 (15%), 256 (22%), 185 (50%). Anal. Calcd for $C_{35}H_{55}N_5O_8$: C, 62.39; H, 8.23; N, 10.39. Found: C, 62.16; H, 8.21; N, 10.08.

B. N-[4-[N-[(1,1-dimethylethoxy)carbonyl]methylamino]piperidine-1-carbonyl]-L-valyl-N-[2,3-dioxo-3-1-methylethoxy-1(S)-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (186 mg, 0.28 mmol) was treated with the periodinane, and the crude product, isolated by chloroform extraction, purified on silica eluted with 2:1 ethyl acetate-hexanes, ethyl acetate, and 1% ethanol in ethyl acetate, giving the title substance (153 mg, 82%). ^1H NMR ($CDCl_3$, 300 mHz) δ 0.83 (d, ca. 2.2H, J= 7 Hz), 0.84 (d, ca. 2.2H, J = 6.5 Hz), 0.9 (m, ca 2H), 0..93 (d, ca. 0.7 Hz, J = ca. 7 Hz), 0.98 (d, ca. 0.7 Hz, J = ca. 7 Hz), 1.28 (d, ca. 4.5 H, J = 6.3 Hz), 1.29 (d, ca. 1.5 H, J = 5.7 Hz), 1.44 (s, 9H), 1.45-1.7 (m, ca 4H), 1.80 (m, 1H), 1.88 (m, 2H), 2.2 (m, ca 1H), 2.68 (s, 3H), 2.78 (m, 2H), 3.01 (dd, 1H, J = 6.5, 13.8 Hz), 3.16 (dd, 1H, J = 6.4, 14.0 Hz), 3.45 (m, 1H), 3.72 (m, 1H), 4.0 (m, ca. 3H), 4.16

(dd, 1H), 4.50 (m, 1H), 5.02 (m, ca 2H), 5.24 (q, 1H), 7.05-7.3 (m, 5H). LSIMS 690 ($MH^+ + H_2O$, 5%), 672 (MH^+, 20%), 340 (100%), 333 (30%), 284 (20%), 256 (20%), 185 (40%). Anal. Calcd for $C_{35}H_{53}N_5O_8 \cdot H_2O$: C, 60.94; H, 8.04; N, 10.15. Found: C, 60.96; H, 7.82; N, 10.29.

C. N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[2,3-dioxo-3-(1-methylethoxy)-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride

By the procedure of example 21h, the product of the preceding Example (120 mg) was deprotected with trifluoroacetic acid and converted to the title hydrochloride, which was triturated with ether, and thus obtained as a colorless solid (92 mg, 84%). ^1H NMR (D_2O, 300 mHz, partial) δ 0.91 (d, 3H, J = 6.7 Hz), 0.96 (d, 3H, J = 6.7 Hz), 1.00 (d, ca. 1H, J = 7.1 Hz), 1.27 (d, 3H, J = 6.5 Hz), 1.32 (d, 3H, J = 5.9 Hz), 1.54 (m, 2H), 1.67 (m, 1H), 1.8-2.1 (m, ca 3H), 2.15 (m, 2H), 2.7 (dd, 1H, J = 11, 14 Hz), 2.74 (s, 3H), 2.95 (m, 2H), 3.18 (dd, 1H, J = 12, 14 Hz), 3.46 (m, 1H), 3.64 (m, 1H), 3.78 (m, 1H), 4.1 (m, 2H), 4.22 (d, 1H, 7.9 Hz), 4.35 (dd, 1H, J = 4.5, 8.5 Hz), 4.48 (dd, 1H, J = 3, 11 Hz), 4.98 (septet, 1H, J = ca. 6 Hz), 7.2-7.4 (m, 5H). LSIMS 572 (70, $M^+ + H$), 458 (45), 354 (70), 315 (65), 250 (100). Anal. Calcd for $C_{30}H_{45}N_5O_6 \cdot HCl \cdot 4H_2O$: C, 52.97; H, 8.00; N, 10.30. Found: C, 53.02; H, 7.33; N, 10.25.

Example 24

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-((1-methyl)ethoxy)-1-(phenylmethyl)propyl]-L-prolinamide

A. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2(R)-hydroxy-3-((1-methyl)ethoxy)-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 16b (250 mg, 0.645 mmol) was coupled with isopropyl 3(S),2(R)-3-amino-2-hydroxy-4- phenylbutanoate (EP 4 814 342, 168 mg, 0.710 mmol) to yield crude product (316 mg) which was chromatographed on silica packed in 2:1 ethyl acetate-hexanes and eluted with ethyl acetate followed by 3%, 10%, and 20% ethanol in ethyl acetate, giving the title substance (242 mg, 62%). LSIMS 607 (40, $M^+ + H$), 335 (100), 281 (70), 221(75), 207(80). Anal. Calcd for $C_{33}H_{42}N_4O_7 \cdot 3/4\ H_2O$: C, 63.91; H, 7.07; N, 9.03. Found: C, 63.95; H, 7.23; N, 8.85.

B. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-((1-methyl) ethoxy)-1(S)-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (172 mg, 0.283 mmol) was treated with the periodinane, and the crude product, isolated by chloroform extraction, was purified on silica eluted with 2%, 4%, and 10% ethanol in dichloromethane giving the title substance as a colorless foam (110 mg, 64%). LSIMS 605 (24, $M^{+}+H$), 333(50), 207(55), 147 (100).

Example 25

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[3-amino-2,3-dioxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

A. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2(R)-hydroxy-3-(amino)-3-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

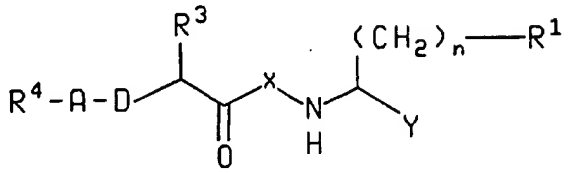
The compound was prepared in a manner according to the procedure described as General Procedure A. The product of Example 16b (250 mg, 0.645 mmol) was coupled with 3(S),2(R)-3-amino-2-hydroxy-4-phenylbutyramide (USP 4 668 769, 164 mg, 0.710 mmol) to yield crude product in unexpectedly low yield (30 mg, 9%). The aqueous layers from the extractions were brought to pH 7 and saturated with NaCl, and the resulting solution was repeatedly extracted with chloroform. These extracts were combined, dried and concentrated giving 102 mg of a yellow foam which was chromatographed on silica eluted with 2%, 6%, and 10% ethanol in dichloromethane giving 26 mg of the title substance.

B. N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[3-amino-2,3-dioxo-1(S)-(phenylmethyl)propyl]-L-prolinamide

The compound was prepared in a manner according to the procedure described as General Procedure C. The product of the preceding Example (22 mg, 0.036 mmol) was treated with the periodinane, and the crude product, isolated by chloroform extraction, was purified on silica eluted with 2%, 4%, 6%, 10%, and 20% ethanol in dichloromethane giving the title substance (7 mg, 32%) LSIMS 564 (30%, $M^{+}+H$), 292 (100%).

CLAIMS

1. A compound of the formula



I

wherein n is one or two;

R^1 is phenyl, naphthyl, (C_3-C_7)cycloalkyl, unsaturated heterocycle, or benzo-fused unsaturated heterocycle; wherein said unsaturated heterocycle is selected from pyrrolyl, pyrrolinyl, furyl, dihydrofuryl, thienyl, dihydrothienyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolinyl, imidazolyl, imidazolinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzofused-unsaturated heterocycle is selected from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl and benzoxazinyl; wherein each of said phenyl, naphthyl, unsaturated heterocycle and benzofused unsaturated heterocycle may optionally be substituted with from one to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C_1-C_5)alkyl, (C_1-C_5)alkoxy, (C_1-C_5)alkylthio, (C_1-C_5)alkylamino, (C_1-C_4)alkylsulfonyl, (C_1-C_5)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl, $-\overset{O}{\overset{\|}{C}}O(C_1-C_5)$alkyl, $-\overset{O}{\overset{\|}{C}}NH_2$, $-\overset{O}{\overset{\|}{C}}NH(C_1-C_5)$alkyl, $-\overset{O}{\overset{\|}{C}}N$-di$(C_1-C_5)$alkyl, and formyl; and wherein said (C_3-C_7)cycloalkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C_1-C_5)alkyl, (C_1-C_5)alkylthio, (C_1-C_5)alkoxy, hydroxy, trifluoromethyl and oxo (O=);

R^3 is (C_1-C_5)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_2)alkyl, (C_1-C_5)alkylthio(C_1-C_2)alkyl, ph nyl, unsaturated heterocycle,

phenyl(C_1-C_2)alkyl, or unsaturated heterocycle(C_1-C_2)alkyl; wherein said unsaturated heterocycle is as defined for R^1; wherein said unsaturated heterocycle(C_1-C_2)alkyl is an unsaturated heterocycle moiety as defined in R^1, wherein any one of the carbon atoms of said unsaturated heterocycle moiety is substituted with (C_1-C_2)alkyl; wherein said (C_1-C_5)alkyl, (C_3-C_6)cycloalkyl(C_1-C_5)alkyl and (C_3-C_6)cycloalkyl may optionally be substituted with one or more fluorine atoms; wherein each of said phenyl, unsaturated heterocycle, phenyl(C_1-C_2)alkyl, and unsaturated heterocycle(C_1-C_2)alkyl may optionally be substituted on the ring atoms with from one to three substituents, said substituents being independently selected from the functionalities set forth in the definition of R^1 for the substituents on said phenyl;

R^4 is selected from the functionalities listed in groups (a) - (d) below:

a) piperazino, piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl and azetidino, wherein any of the carbon atoms of said piperazino may optionally be substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, (C_1-C_5)alkylthio(C_1-C_3)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, and (C_1-C_5)dialkylamino(C_1-C_3)alkyl; wherein the nitrogen in the 4 position of said piperazino may optionally be substituted with (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_2-C_4)alkyl, hydroxy(C_2-C_4)alkyl, amino(C_2-C_4)alkyl, (C_1-C_5)alkylamino(C_2-C_4)alkyl, (C_1-C_5)dialkylamino(C_2-C_4)alkyl, and 2,2,2-trifluoroethyl; wherein any of the carbon atoms of said piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl and azetidino may optionally be substituted with one or two substituents, said substituents being independently selected from chloro, bromo, fluoro, hydroxy, (C_1-C_5)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, (C_1-C_5)alkoxy(C_1-C_3)alkyl, (C_1-C_5)alkoxy, (C_1-C_5)alkoxy(C_1-C_3)alkoxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, (C_1-C_5)alkylthio, oxo (O=), unsaturated heterocycle, azetidino, pyrrolidino, piperidino, morpholino, 4-oxopiperdino, 4-hydroxypiperidino and piperazino, wherein the nitrogen in the 4 position of said piperazino may optionally be substituted with (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_2-C_4)alkyl, hydroxy(C_2-C_4)alkyl, amino(C_2-C_4)alkyl, (C_1-C_5)alkylamino(C_2-C_4)alkyl, (C_1-C_5)dialkylamino(C_2-C_4)alkyl, or 2,2,2 trifluoroethyl; wherein said unsaturated heterocycle is as defined in R^1; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from th

functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle;

b) 4-morpholino, 4-thiomorpholino, 1-oxothiomorpholino, and 1,1-dioxothiomorpholino; wherein any of the carbon atoms of said 4-morpholino, 4-thiomorpholino, 1-oxothiomorpholino, and 1,1 dioxothiomorpholino may optionally be substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, (C_1-C_5)alkylthio(C_1-C_3)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl and (C_1-C_5)dialkylamino(C_1-C_3)alkyl;

c) (C_1-C_7)alkyl and (C_3-C_7)cycloalkyl; wherein said (C_3-C_7)cycloalkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from halo, hydroxy, (C_1-C_5)alkoxy, (C_1-C_5)alkoxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, (C_1-C_5)alkylthio(C_1-C_3)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, (C_1-C_5)alkoxy(C_1-C_3)alkyloxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, (C_1-C_5)alkylthio, azetidino, pyrrolidino, piperidino, piperazino, 4-(C_1-C_5)alkylpiperazino, morpholino, thiomorpholino, oxothiomorphilino, dioxothiomorpholino, 4-oxopiperidino, 4-hydroxypiperidino, and unsaturated heterocycle, wherein said unsaturated heterocycle is defined as in R^1; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle; wherein said (C_1-C_7)alkyl may optionally be substituted with one to three substituents, said substituents being independently selected from halo, hydroxy, (C_1-C_5)alkoxy, (C_1-C_5)alkoxy(C_1-C_3)alkyloxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, (C_1-C_5)alkylthio, azetidino, pyrrolidino, piperidino, piperazino, 4-(N)-(C_1-C_5)alkylpiperazino, morpholino, thiomorpholino, oxothiomorpholino, dioxothiomorpholino, 4-oxopiperidino, 4-hydroxypiperidino, and unsaturated heterocycle; wherein said unsaturated heterocycle is defined as in R^1; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle;

d) (R^5E)-, wher in E is oxygen, -NH or -N(C_1-C_5)alkyl, wh r in R_5 is $(C_1-$

C_5)alkyl, 2,2,2 trifluoroethyl, $R^7(C_2\text{-}C_4)$alkyl, $R^7C(=O)(C_2\text{-}C_4)$alkyl, $R^7C(=O)\text{-}N(C_1\text{-}C_5\text{alkyl})\text{-}(C_2\text{-}C_4)$alkyl, unsaturated heterocycle$(C_2\text{-}C_4)$alkyl, amino$(C_2\text{-}C_4)$alkyl, -C_4)alkyl, $(C_1\text{-}C_5)$alkoxy$(C_2\text{-}C_4)$alkyl or hydroxy$(C_2\text{-}C_4)$alkyl; wherein said unsaturated heterocycle$(C_2\text{-}C_4)$alkyl is an unsaturated heterocycle moiety as defined in R^1, wherein one of the ring atoms of said unsaturated heterocycle moiety of said unsaturated heterocycle$(C_2\text{-}C_4)$alkyl so defined is substituted with $(C_2\text{-}C_4)$alkyl; wherein said unsaturated heterocycle$(C_2\text{-}C_4)$alkyl may optionally be substituted on any of the ring atoms with from one to three substituents independently selected from the functionalities set forth in the definition of R^1 for the substituents on said unsaturated heterocycle;

R^7 is azetidino, pyrrolidino, piperidino, piperazino, 4-(N)-$(C_1\text{-}C_5)$alkylpiperazino, thiomorpholino, oxothiomorpholino, dioxothiomorpholino or morpholino;

A is carbonyl or sulfonyl;

D is NH, N$(C_1\text{-}C_5)$alkyl, CH_2, oxygen, CH(OH), or CH-O-$(C_1\text{-}C_5)$alkyl;

X is proline, 2-piperidinecarboxylic acid or 2-azetidinecarboxylic acid, wherein said proline, 2-piperidinecarboxylic acid and 2-azetidinecarboxylic acid may optionally be substituted with one or two substituents, said substituents being independently selected from bromine, chlorine, fluorine, $(C_1\text{-}C_5)$alkyl, $(C_1\text{-}C_3)$alkoxy, oxo, and hydroxy;

Y is BF_2, $B(OM)_2$, $-C(=O)\text{-}Z$ or $-C(OH)_2Z$, wherein M is hydrogen, or $(C_1\text{-}C_5)$alkyl, wherein the two M substituents may optionally form, together with the boron atom and the two oxygen atoms to which they are attached, a saturated heterocyclic ring containing the boron atom, 2 oxygen atoms and 2 or 3 carbon atoms, and wherein any of the carbon atoms of said heterocyclic ring may optionally be substituted with one or two $(C_1\text{-}C_5)$alkyl groups;

Z is selected from CF_2R^{11}, $CF_2C(=O)\text{-}N(R^{13})\text{-}R^{12}$, $-C(=O)\text{-}N(R^{13})\text{-}R^{12}$, $-C(=O)\text{-}O\text{-}R^{12}$ or a

heterocycle selected from 2-oxazolyl, 2-thiazolyl, 2-imidazolyl, 2-thienyl, 2-furyl, 2-pyrrolyl, 5-tetrazolyl, 2-benzothiazolyl, 2-benzoxazolyl, 2-benzimidazolyl, 2-benzofuryl, 2-benzothienyl and 2-indolyl; wherein said heterocycle may optionally be substituted with one to three substituents, said substituents being independently selected from (C_1-C_3)alkoxy, bromo,

chloro, fluoro, (C_1-C_3)alkyl, hydroxy, amino, nitro, cyano, -$\overset{O}{\overset{\|}{C}}$O($C_1$-$C_5$)alkyl, -$\overset{O}{\overset{\|}{C}}$$NH_2$,

formyl, (C_1-C_5)alkylthio, (C_1-C_5)alkylamino, -CF_3, (C_1-C_4)alkyl-SO_2-, trifluoromethyl, and (C_1-C_5)dialkylamino;

R^{11} is hydrogen, fluorine, (C_1-C_5)alkyl, (C_1-C_6)perfluoroalkyl, amino (C_1-C_5)alkyl, (C_1-C_5)alkylamino(C_1-C_5)alkyl, di(C_1-C_5)alkylamino(C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_5)-alkyl or hydroxy(C_1-C_5)alkyl;

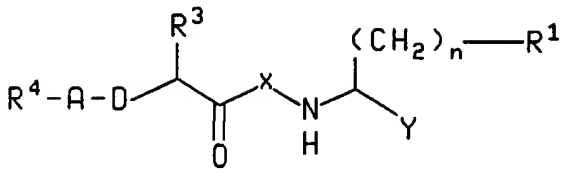
R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_5)alkyl, (C_3-C_5)alkenyl, and R^7(C_2-C_4)alkyl, wherein R^7 is defined as above;

with the proviso that (a) no carbon alpha to a ring nitrogen in the substituent R^4 may be directly bonded to a halogen, oxygen or nitrogen substituent, (b) when X is substituted proline, 2-piperidinecarboxylic acid or 2-azetidinecarboxylic acid, then no fluorine, oxo, (C_1-C_3)alkoxy or hydroxy substituent is present on either of the ring carbon atoms adjacent to the nitrogen atom of said proline, 2-piperidinecarboxylic acid or 2-azetidinecarboxylic acid, and (c) the compound of formula I can not be defined as a compound wherein n is one, R^1 is phenyl, R^3 is phenyl(C_1-C_2)alkyl, R^4 is (R^5E)- wherein E is oxygen and R^5 is (C_1-C_5)alkyl, A is carbonyl, D is NH, X is proline and Y is $B(OM)_2$.

2. A compound according to claim 1 with the additional proviso that (d) the compound of formula I can not be defined as a compound wherein n is one, R^1 is phenyl, R^3 is phenyl(C_1-C_2)alkyl, R^4 is unsubstituted (C_1-C_4)alkyl, A is carbonyl, D is NH, X is proline and Y is $B(OM)_2$.

3. A compound according to claim 1 with the additional proviso that (d) the compound of formula I can not be defined as a compound wherein n is one, R^1 is phenyl, R^3 is phenyl(C_1-C_2)alkyl, R^4 is unsubstituted (C_1-C_5)alkyl, A is carbonyl, D is NH, X is proline and Y is BF_2.

4. A compound of the formula



I

wherein n is 1;

R^1 is phenyl or (C_3-C_7)cycloalkyl, wherein said phenyl may optionally be substituted with from one to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C_1-C_5)alkyl, (C_1-C_5)alkoxy, (C_1-C_5)alkylthio, (C_1-C_5)alkylamino, (C_1-C_4)alkylsulfonyl, (C_1-C_5)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,

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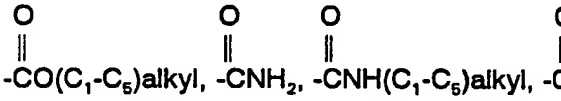
‖ ‖ ‖ ‖
$-CO(C_1-C_5)$alkyl, $-CNH_2$, $-CNH(C_1-C_5)$alkyl, $-CN$-di(C_1-C_5)alkyl, and formyl; and wherein said (C_3-C_7)cycloalkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C_1-C_5)alkyl, (C_1-C_5)alkylthio, (C_1-C_5)alkoxy, hydroxy, trifluoromethyl and oxo (O=);

R^3 is (C_1-C_5)alkyl, hydroxy(C_1-C_5)alkyl, (C_1-C_5)alkoxy(C_1-C_2)alkyl, (C_1-C_5)alkylthio(C_1-C_2)alkyl, phenylmethyl, 4-imidazolylmethyl or 4-thiazolylmethyl; wherein any of the carbon atoms of said (C_1-C_5)alkyl may optionally be substituted with one or more fluorine atoms; and wherein from one to three carbon atoms of the phenyl moiety of said phenylmethyl may optionally be substituted with any of the functionalities set forth in the definition of R^1 above for the substituents on said phenyl;

R^4 is selected from the functionalities listed in groups (a)-(d) below:

a) piperidino, pyrrolidino, 3-azabicyclo[3.1.0]hex-3-yl and azetidino; wherein the nitrogen in the 4-position of said piperazino may optionally be substituted with (C_1-C_5)alkyl, (C_1-C_5)alk xy(C_2-C_4)alkyl, hydroxy(C_2-C_4)alkyl, amino(C_2-C_4)alkyl, (C_1-C_5)alkylamino(C_2-C_4)alkyl, (C_1-C_5)dialkylamino(C_2-C_4)alkyl, or 2,2,2 trifluor thyl; wherein any of the ring carbon atoms of said pip razino, pip ridino, pyrrolidino, 3-

azabicyclo[3.1.0]hex-3-yl and azetidino may optionally be substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, amino (C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, hydroxy, oxo (O=), (C_1-C_5)alkoxy(C_1-C_3)alkoxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-C_5)alkylpiperazino, morpholino, and unsaturated heterocycle; wherein said unsaturated heterocycle is selected from pyrrolyl, pyrrolinyl, furyl, dihydrofuryl, thienyl, dihydrothienyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolinyl, imidazolyl, imidazolinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzofused-unsaturated heterocycle is selected from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl and benzoxazinyl; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C_1-C_5)alkyl, (C_1-C_5)alkoxy, (C_1-C_5)alkylthio, (C_1-C_6)alkylamino, (C_1-C_4)alkylsulfonyl, (C_1-C_5)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,



-CO(C_1-C_5)alkyl, -CNH_2, -CNH(C_1-C_5)alkyl, -CN-di(C_1-C_5)alkyl, and formyl;

b) morpholino optionally substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, and (C_1-C_5)dialkylamino(C_1-C_3)alkyl;

c) (C_1-C_7)alkyl and (C_3-C_7)cycloalkyl; wherein said (C_1-C_7)alkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-C_5)alkylpiperazino and morpholino; wherein said (C_3-C_7)cycloalkyl may optionally be substituted with one to three substituents, said substituents being independently selected from amino, (C_1-C_6)alkylamino, (C_1-C_5)dialkylamino, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-

C_5)alkylpiperazino, morpholino and unsaturated heterocycle, wherein said unsaturated heterocycle is as defined in the definition of unsaturated heterocycle in R^4(a) above; wherein said unsaturated heterocycle may optionally be substituted with from one to three substituents independently selected from the functionalities set forth in the definition of unsaturated heterocycle in R^4(a) above; and

d) (R^5E)-, wherein E is oxygen or -N(C_1-C_5)alkyl, and wherein R^5 is (C_1-C_5)alkyl, 2-(pyridyl)ethyl, di(C_1-C_5)alkylaminoethyl, di(C_1-C_5)alkylaminopropyl, 2-(R^7C)ethyl or 2-[R^7CN(C_1-C_5)alkyl]ethyl;

R^7 is azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-C_5)alkylpiperazino, thiomorpholino, oxothiomorpholino, dioxothiomorpholino or morpholino;

A is carbonyl or sulfonyl;

D is NH, CH_2 or oxygen;

X is proline;

Y is -C-Z or $-C(OH)_2Z$;

Z is CF_3, CO_2R^{12}, -C-N-R^{12}, $-CF_2$CN-R^{12},

or a heterocycle selected from 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl; wherein said 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl may optionally be substituted with from one to three substituents independently selected from (C_1-C_3)alkoxy, bromo,

chloro, fluoro, (C_1-C_3)alkyl, hydroxy, amino, nitro, cyano, -CO(C_1-C_5)alkyl, -CNH_2,

formyl, (C_1-C_5)alkylthio, (C_1-C_5)alkylamino, $-CF_3$, (C_1-C_4)alkyl-SO_2-, trifluoromethyl, and (C_1-C_5)dialkylamino;

R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_5)alkyl, (C_3-C_5)alkenyl, and R^7(C_2-C_4)alkyl, wherein R^7 is defined as above;

with the proviso that (a) no carbon alpha to a ring nitrogen in the substituent R^4 may be directly bonded to a halogen, oxygen or nitrogen substituent, (b) when X is substituted proline, then no fluorine, oxo, (C_1-C_3)alkoxy or hydroxy substituent is present on either of the ring carbon atoms adjacent to the nitrogen atom of said proline, and (c) when E is oxygen R^5 is (C_1-C_5)alkyl; and (d) when E is $N(C_1-C_5)$alkyl, R^5 is selected

from 2-(pyridyl)ethyl, di(C_1-C_5)alkylaminoethyl, di(C_1-C_5)alkylaminopropyl, 2-(R^7C(=O))ethyl and 2-[R^7CON(C_1-C_5)alkyl]ethyl.

5. A compound according to claim 4 wherein R^1 is cyclohexyl or phenyl;

R^3 is (C_1-C_5)alkyl, phenylmethyl, 4-imidazolylmethyl, or 4-thiazolylmethyl;

R^4 is piperazino, 4-N-(C_1-C_5)alkylpiperazino, morpholino, piperidino, 2-(C_1-C_5)dialkylamino(C_1-C_3)alkylmorpholino, or (C_3-C_7)cycloalkyl; wherein said piperidino may optionally be substituted with one or two substituents, said substituents being independently selected from (C_1-C_5)alkyl, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, hydroxy, oxo, (C_1-C_5)alkoxy, (C_1-C_5)alkoxy(C_1-C_3)alkyloxy, amino, (C_1-C_6)alkylamino, (C_1-C_5)dialkylamino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, 4-N-(C_1-C_5)alkylpiperazino and unsaturated heterocycle; wherein said unsaturated heterocycle is as defined as in the definition of R^4(a) in claim 2; wherein said unsaturated heterocycle may optionally be substituted with one to three substituents independently selected from the functionalities set forth in the definition of R^4(a) in claim 2 for the substituents on said unsaturated heterocycle; wherein said (C_3-C_7)cycloalkyl may optionally be substituted with from one to three substituents, said substituents being independently selected from hydroxy, oxo (=O), (C_1-C_5)alkoxy, amino, (C_1-C_5)alkylamino, (C_1-C_5)dialkylamino, amino(C_1-C_3)alkyl, (C_1-C_5)alkylamino(C_1-C_3)alkyl, (C_1-C_5)dialkylamino(C_1-C_3)alkyl, azetidino, pyrrolidino, piperidino, piperazino, 4-N-(C_1-C_5)piperazino, morpholino, and unsaturated heterocycle; wherein said unsaturated heterocycle is as defined as in the definition of R^4(a) in claim 2; wherein said unsaturated heterocycle may optionally be substituted with one to three substituents independently selected from the functionalities set forth in the definition of R^4(a) in claim 2 for the substituents on said unsaturated heterocycle;

A is carbonyl or sulfonyl;

D is NH, CH_2 or oxygen;

X is proline;

Y is $-\overset{O}{\overset{\|}{C}}-Z$ or $-C(OH)_2Z$;

Z is CF_3, CO_2R^{12}, $-\overset{O}{\overset{\|}{C}}-\underset{R^{13}}{\underset{|}{N}}-R^{12}$, $-CF_2\overset{O}{\overset{\|}{C}}\underset{R^{13}}{\underset{|}{N}}-R^{12}$,

or a heterocycle selected from 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl; wherein said 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl, 2-furyl, 2-benzofuryl, 2-thienyl and 2-benzothienyl may optionally be substituted with from one to three substituents independently selected from (C_1-C_3)alkoxy, bromo,

chloro, fluoro, (C_1-C_3)alkyl, hydroxy, amino, nitro, cyano, $-\overset{O}{\overset{\|}{C}}O(C_1-C_5)$alkyl, $-\overset{O}{\overset{\|}{C}}NH_2$,

formyl, (C_1-C_6)alkylthio, (C_1-C_5)alkylamino, $-CF_3$, (C_1-C_4)alkyl-SO_2-, trifluoromethyl, and (C_1-C_5)dialkylamino;

R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_5)alkyl, (C_3-C_5)alkenyl, and $R^7(C_2-C_4)$alkyl, wherein R^7 is defined as above;

with the proviso that (a) no carbon alpha to a ring nitrogen in the substituent R^4 may be directly bonded to a halogen, oxygen or nitrogen substituent,and (b) when X is substituted proline, then no fluorine, oxo, (C_1-C_3)alkoxy or hydroxy substituent is present on either of the ring carbon atoms adjacent to the nitrogen atom of said proline.

6. A compound of the formula I according to claim 1 wherein that compound is

N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[2,3-dioxo-3-m thoxy-1-(phenylmethyl)propyl]-L-prolinamide;

N-[(1,1-dimethyethoxy)carbonyl]-L-valyl-N-[2,3-dioxo-3-methoxy-1-(phenylmethyl)propyl]-L-prolinamide;

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride;

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[3,3,3-trifluoro-2-oxo-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride;

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[2,3-dioxo-3-1-methylethoxy-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride;

N-[4-[N-methylamino]piperidine-1-carbonyl]-L-valyl-N-[2,3-dioxo-3-1-methylethoxy)-1(S)-(phenylmethyl)propyl]-L-prolinamide hydrochloride;

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-((1-methyl)ethoxy)-1-(phenylmethyl)propyl]-L-prolinamide; or

N-(4-oxopiperidine-1-carbonyl)-L-phenylalanyl-N-[2,3-dioxo-3-((1-methyl) ethoxy)-1(S)-(phenylmethyl)propyl]-L-prolinamide.

7. A method of treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease, diabetic renal disease, and non-diabetic renal disease, comprising administering to a mammal in need of such treatment a chymase inhibiting effective amount of a chymase inhibiting compound, or pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease, diabetic renal disease, and non-diabetic renal disease, comprising a chymase inhibiting effective amount of a chymase inhibiting compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. A method for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease, diabetic renal disease, and non-diabetic renal disease, which comprises administering to a mammal in need of such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disease.

10. A pharmaceutical composition for tr ating or preventing a diseas selected from hypertension, cardiac and left ventricular hyp rtrophy, coronary artery dis as , diabetic renal diseas , and non-diabetic r nal disease, comprising an amount

of a compound of the formula I that is effective in treating or preventing such disease, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. A method for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease, diabetic renal disease, and non-diabetic renal disease, which comprises administering to a mammal in need of such treatment a chymase inhibiting amount of a compound of the formula I or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition for treating or preventing a disease selected from hypertension, cardiac and left ventricular hypertrophy, coronary artery disease, diabetic renal disease, and non-diabetic renal disease, comprising a chymase inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/03625

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K5/02; C07K5/06; C07D401/06; A61K37/64
A61K31/435

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	WO,A,9 220 357 (MERRELL DOW PHARMACEUTICALS INC.) 26 November 1992 see example I page 35 line 26 - line 34 ---	1-6
X	EP,A,0 410 411 (MERRELL DOW PHARMACEUTICALS INC.) 30 January 1991 see page 8, line 14 - line 36; claims 4-5,45-49 ---	1-12
X	EP,A,0 145 441 (E.I. DU PONT DE NEMOURS AND COMPANY) 19 June 1985 see claims; examples 11,35; table 2 ---	1-12
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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 AUGUST 1993	23 -09- 1993
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FUHR C.K.B.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	BIOCHEMISTRY vol. 27, no. 20, 4 October 1988, EASTON, PA US pages 7682 - 7688 C.A. KETTNER 'Kinetic Properties of the Binding of alpha-Lytic Protease to Peptide Boronic Acids' see introduction on pages 7682-7683 see table II	1-6
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 33, no. 1, January 1990, WASHINGTON US pages 394 - 407 N.P. PEET ET AL. 'Synthesis of Peptidyl Fluoromethyl Ketones and Peptidyl alpha-Keto Esters as Inhibitors for Porcine Pancreatic Elastase, Human Neutrophil Elastase, and Rat and Human Neutrophil Cathepsin G' see scheme II on page 395, formulas 9a and 9b see table I on page 397, compounds 9a, 29, 9b and 25 see page 402, right column, paragraph 3 -paragraph 4 see page 405, left column, paragraph 3	1-6
X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS vol. 166, no. 2, 30 January 1990, DULUTH, MINNESOTA US pages 595 - 600 S. MEHDI ET AL. 'THE INHIBITION OF HUMAN NEUTROPHIL ELASTASE AND CATHEPSIN G BY PEPTIDYL 1,2-DICARBONYL DERIVATIVES' see page 595, paragraph 2 - page 596, paragraph 1; figure 1	1-6
A	JOURNAL OF BIOLOGICAL CHEMISTRY vol. 265, no. 36, 25 December 1990, BALTIMORE, MD US pages 22348 - 22357 H. URATA ET AL. 'Identification of a Highly Specific Chymase as the Mayor Angiotensin II-forming Enzyme in the Human Heart' see the whole document	1-12

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF BIOLOGICAL CHEMISTRY vol. 266, no. 29, 15 October 1991, BALTIMORE, MD US pages 19192 - 19197 A. KINOSHITA ET AL. 'Multiple Determinants for the High Substrate Specificity of an Angiotensin II-forming Chymase from the Human Heart' see the whole document -----	1-12

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9303625
SA 73720

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 25/08/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	2021660	27-01-91
		CN-A-	1049016	06-02-91
		JP-A-	3086852	11-04-91
EP-A-0145441	19-06-85	US-A-	4499082	12-02-85
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